

	Editorial	23	Extended Maxillectomy by Transmandibular Approach <i>S.S. Chatni, R. Sharan, S. Iyer, M.A. Kuriakose</i>
2	Commercialization of Medicine <i>H. Kumar</i>		
	Spiritual Message	29	Clinical Whodunit Nasal Cure for a Myopathy – A Neuroendocrine Puzzle? <i>G. Siby, U.K. Syam, A. Anandkumar, Hiran, G. Aneesh</i>
3	Patience <i>Swami Paramatmananda Puri</i>		
	Review Article	33	Quiz Radiology Quiz <i>Chandramohan, R. Kannan, S. Moorthy</i>
5	Carcinoma of the Ovary <i>Chithrathara</i>		
	Practical Approach	34	Case Reports Rhinocerebral Mucormycosis in a Patient with Diabetic Nephropathy <i>A. Mathew, J.C. Varghese, P. Nair, V.N. Unni</i>
9	Comprehensive Rehabilitation: A New Dawn for the Disabled <i>J.N. Panicker</i>		
	Viewpoint	37	Mutiple Endocrine Neoplasia – 2B <i>N.M. Detroja, B. Nisha, A.G. Unnikrishnan</i>
13	Caution! Counterfeit Medicines are on the Rise <i>B.P. Rao</i>		
	Original Articles	41	Literature Scan Cases, Evidence and Verdicts - The Glitazone Controversy <i>T. Roy, T. Rony, A.N. Babu</i>
18	Analysis of GSTM1 and CYP1A1 Genes Tropical Chronic Pancreatitis <i>A.G. Unnikrishnan, S. Ramachandran, M.R. Pillai, H. Kumar, P. Nair, R.V. Jayakumar, U. Guruprasad, R. Nandakumar, T. Joseph, I. Hariharan, V. Balakrishnan</i>		

Editorial Board

Patrons

Swami Amrita Swaroopananda Puri
 Dr. Prem Nair
 Mr. Ron Gottsegen
 Dr. D.M. Vasudevan

Chief Editor

Dr. Harish Kumar

Associate Editors

Dr. Anand Kumar
 Dr. Sudhindran

Editorial Assistance

Dr. V.P. Praveen
 Dr. P. Gowri

Editorial Board Members

Dr. V. Balakrishnan
 Mr. Sudhakar Jayaram
 Dr. Dilip Panikar
 Dr. Prakash Kamath
 Dr. S.K. Nair
 Dr. Vaidyanathan
 Dr. M.G.K. Pillai
 Dr. Subramanian
 Dr. Kanthaswami
 Dr. Abraham Kuriakose

Publications Officer

Mrs. Jaya Sudhir Maharshi

Visualiser

Mr. Biju Chembalayath

Cover Illustrations

Mr. Biju Chembalayath
 Mrs. Rajalakshmi Remesh
 Dept. of Graphics, AIMS

Commercialization of Medicine

Harish Kumar

People come to see a doctor when they are feeling ill, either physically or mentally. The duty of a physician is to then prescribe the necessary remedies to restore the equilibrium and make the person feel better. It is a sacred duty – the aim of which is to take an individual from a state of “ashanti” to “shanti”. Once he is healed or better the patient will gratefully compensate the physician in cash or kind, as per his means. The physician gains not only monetarily, but also is enriched by the gratefulness and good wishes of the diseased person and the family of those whom he has healed. The whole focus of the patient-physician interaction is that the patient must feel better, and there is an attitude of surrender and trust on the part of the patient.

But in today’s world, medicine has become commercialized. Pharmaceutical and other commercial companies are interested only in profits and they can generate, and sustain these profits only with the active support of the doctor community. It is a well known, but not often admitted, reality that commercial interests frequently dominate prescription patterns not only in India, but also all over the world. This has caused a subtle shift in the attitude of many doctors whose primary focus is now on the commercial gains from the profession and the service provided to the patient has become secondary. The main casualty in this new commercial scenario is the doctor-patient trust. Patients are increasingly suspicious of the intentions of doctors and ever-increasing medico-legal litigations are the outward symptom of this malaise. The ‘trust’ and ‘surrender’ have been replaced by a business like transaction, which takes away the sacredness of healing. The other side of the coin is the benefit that has accrued to the science of medicine due to this commercialization. Enormous sums of money are being pumped into research in various areas of medicine by commercial organizations and our treatment and investigation modalities are improving at an ever-increasing pace.

The majority of physicians are not commercial and there is still hope if efforts are made to better physician-patient bonding. But unfortunately, today the success of a doctor is measured by the amount of material wealth he has accumulated from the practice of his profession. If this trend continues then doctors and commercial organizations doing business in the medical field may become richer but the profession and its public image are becoming poorer by the day.

Patience

Swami Paramatmananda Puri

Working in the healthcare field, one has a great deal of interaction with other people – doctors, nurses, patients and their families, administrators and so on, and therefore, one has vast opportunities for self-improvement. Amma says that life is like a school and every situation gives us a chance to learn about our self and the world in which we live. We should always try to remain conscious of that fact as we travel through life. One of the essential qualities that we need to develop if we want our life to be successful is patience, and there is no shortage of opportunities for us to do so in the healthcare setting.

Unfortunately, patience is hard to come by in those of us who have been raised in an increasingly comfortable and technological world. Modern life seems to be about speed, enjoyment and comfort. We go to great lengths to make sure that we do not have to undergo any inconvenience, delay or boredom. We find waiting and adjusting with other people and circumstances to be very painful. Our mind is like a child's mind – impatient and impetuous. And all this impatience leads to uncontrollable anger and pain.

We have heard from elders that when life was not so fast and comfortable, people were a lot more patient and a lot less angry. They were also willing to do a lot more for refining their personality and for making spiritual progress. Apparently, the ancient culture of India still has a few things to teach us!

Anger can be seen everyday at home, in school, at the workplace, when shopping, and even on the road. We have all heard of road rage. This is an instance of an abnormal lack of patience resulting in intense anger. We may not feel that we are an angry person, but a naturally self-controlled person is a rarity. Even so-called spiritual people can have a lot of hidden anger. Sometimes, out of compassion, mahatmas will show us how much anger we really have so that we can become aware of it and try to improve.

There once was a sadhu named Suthra who was an exceptionally bold and compassionate person. One day, a friend came to him and said, "A famous holy man who is very much revered by everybody in this neighbourhood has come. Let us go and see him."

Suthra agreed, and they walked to the holy man's hut, greeting him upon their arrival by bowing down. The holy man invited them to be seated. After a few minutes silence, Suthra asked the holy man, "Have you any fire? I need some."

The holy man said, "No, I have no fire here at present."

Again, after a few minutes of silence, Suthra again asked the holy man, "O sadhu, have you any fire?"

"I have already told you that I have none," said the holy man, slightly annoyed.

But this did not seem to make any impression on Suthra. He again asked the man, "Sir, I have great need of some fire, so let me have some."

At this, the holy man became really irritated and replied with great heat, "O foolish man! Please stop asking me for fire! Can't you understand what I say? I have told you three times that I do not have any fire. Isn't that enough? Or will you go on repeating the same stupid question over and over again?"

Suthra kept silent while the holy man scolded him. Then he said, "Brother, I really need some fire. Are you absolutely sure that you don't have any?"

Now thoroughly enraged, the sadhu stood up and picked up a stick. He beat Suthra with it until the stick broke. Suthra then smiled and said, "My question is now answered. I saw and smelled some smoke when I entered your presence, and so I knew that there was fire here. And now, as anyone can see, the fire has blazed up and is burning with angry flames. Yet strangely enough, you still maintain that you have none."

Understanding now that Suthra was referring to his anger, the sadhu immediately calmed down. Hanging his head in shame, he said in a humble voice, "Thank you, Mahatmaji, for your lesson. I will take it to heart and try to mend my ways."

In order to purify our mind, we must first know what is there in our mind to purify. This is the function of divine grace. A mahatma will let us know what is inside us either through his/her mere presence or through our circumstances. Amma knows that we are impatient and have a lot of anger as well as pride. She uses "crowds" as one of the means to purify our minds. Due to the huge crowds that come to see Amma, we must wait a long time in order to have her darshan. That itself gives us a chance to develop patience, humility and devotion. Amma does not just make *us* be patient, but is herself the very image of patience. Look how she patiently sits until the last person has had her darshan. Many of us have seen her begin darshan at 8:00pm and continue until the next day at noon, not getting up even for a minute. Who can or will do such a thing, giving up sleep and

comfort day after day? Who else can listen to problems for hours on end? Who can sincerely smile continuously? Who else can travel around India and the world for 8 months in the year, keeping up an impossible schedule? If we can't learn a little patience from such a being, we are really a hopeless case. One may search for a long time, but one would be hard put to find a role model such as Amma who practices what she preaches.

Amma tells of seeing people waiting all day in line at the government hospital in order to see a doctor. But for making a bit of spiritual progress or self-improvement, most people have no patience. Many of us want everything right now. People come to Amma and insist that they should have darshan immediately or that their problems should disappear without the least delay! They have no time to hang around. With such a lack of patience, what benefit will they get from Amma's company?

In relation to the Highest Truth, without patience, we cannot gain the direct experience of our true self, the Atma. The ever-bubbling restless mind prevents us from doing so. The state that Amma demonstrates in her own life and which she wants us to also experience is one of perfect stillness, peace, *shanti*.

Instead of getting angry whenever we must wait or when we meet with resistance, let us use such situations to practice patience. Let us think of Amma's example of natural patience and try to follow in her footsteps. Then we will find every difficulty becoming an opportunity for spiritual practice. When we naturally become as patient as Amma, then we have reached a lasting goal. We will be happy and have great satisfaction, and we will make others happy too.

Carcinoma of the Ovary

Chithrathara

ABSTRACT

In India, ovarian carcinoma, the second most common gynecological malignancy, is showing a rising trend. Epithelial ovarian carcinoma (EOC) forms about 90% of malignant ovarian tumors. The retrospective data and the meta-analysis favoured upfront surgical cytoreduction. Neoadjuvant chemotherapy (NAC) and interval surgery has come into practice to reduce the incidence of non-therapeutic laparotomies. Sound clinical judgement and CT scan can reliably predict the inoperability and helps to select patients for NAC. Any form of minimally invasive surgery is to be used with caution. Literature also projects the surgeon as an independent prognostic factor and the surgery is best contemplated in centers of excellence. Early disease requires comprehensive surgical staging. Borderline serous tumors require counselling for restaging versus surveillance. Changing the cycling of drugs, targeted and tailored therapy are promising future treatment options.

INTRODUCTION

Ovarian cancer is the second most common gynecological cancer. Epithelial ovarian cancers (EOC) constitute 90% of malignant ovarian tumors. Most unfortunately 3/4th of the patients are diagnosed at an advanced stage with disseminated intra-abdominal disease. Even though complete remission can be achieved in 90% of patients, relapse is the rule. Relapses are salvaged with repeated cycles of chemotherapy and surgery is used only in selected cases. The longer the disease free interval, the better the response to further chemotherapy. The discovery of newer and newer chemotherapy molecules

Dept. of Surgical Oncology, AIMS, Kochi.

has converted ovarian carcinoma to a 'chronic disease'. The cachectic patient finally succumbs to death due to uncontrolled intra-abdominal disease with multiple level intestinal obstructions.

INCIDENCE

EOC is a disease of senescent ovary. The age adjusted incidence rates increase from 15/100,000 to 57/100,000 during the 8th decade. Age adjusted incidence rates in Kerala are little lower than western countries. The population-based data available from Thiruvananthapuram showed incidence rates of 5.3/100,000 in the urban area and 3.5/100,000 in rural area. Hospital based cancer registry shows that it is 6/100 women cancers.

HEREDITARY OVARIAN CARCINOMA

5-10% of ovarian cancers are linked to genetic predisposition. The breast-ovarian cancer syndrome accounts for approximately 90% of hereditary ovarian cancer cases and is frequently associated with BRCA1 & BRCA2. The hereditary non-polyposis colorectal cancer accounts for 5% of cases. Firm conclusions could not be drawn on the benefit of genetic testing and early detection¹. Presently the most effective strategy in the prevention of ovarian carcinoma is prophylactic bilateral oophorectomy, which also causes a substantial reduction in breast cancer risk².

MANAGEMENT OF EPITHELIAL OVARIAN TUMORS

Aggressive surgical cytoreduction and platinum based chemotherapy forms the mainstay of management of EOC. Even though there are no ran-

domized trials, literature is replete with retrospective data, which gives ample evidence for the use of upfront cytoreductive surgery. The results of two meta-analysis also favour primary surgery. It gives accurate initial staging and there is theoretical advantage of better action of chemotherapy based on Gompertzian model. Removal of the tumor in total and a comprehensive surgical staging is indicated in early stage ovarian cancer. Keyhole and vaginal surgery, limited incisions, etc. are to be avoided especially in suspected early stage ovarian malignancy since these compromise cure and endanger the life of the woman.

The prognostic determinants include stage, histological subtype and grade, medical co-morbidities, performance status, response to chemotherapy and post-operative residual disease. The only consistent alterable variant is post-operative residual disease. So it is the first surgery that determines the outcome. Many are of the opinion that post-operative residual disease is a reflection of biological aggressiveness of the tumor. But Eisenkope and others have demonstrated that the surgical effort and accompanying survival is surgeon dependent³. The approach and thus the result can vary among surgeons depending on their perspective and philosophy⁴.

The GOG studies give important insights into the impact of cytoreductive surgery in ovarian carcinoma. They defined the optimal debulking surgery as the removal of all gross or visible tumor. When patient was left with no residual tumor a progression free survival of 40 months was observed, compared to 20 months in

patients with residual disease of less than 1 cm. It is shown that a possibly superior chemotherapeutic regimen containing taxanes cannot compensate for the tumor left behind after surgery. (19 JSO)

The maximum goal of cytoreductive (debulking) surgery should be the complete removal of all visible disease and the minimum is to reduce the tumor to less than 1 cm (optimal debulking). To meet this target one may often have to go for intestinal resections, rarely splenectomy, peritoneal excisions including diaphragmatic peritoneum and genito-urinary tract resections. Surgical procedures, which impair quality of life, for e.g. ostomies, should be avoided as far as possible. Precise and more expeditious removal of widespread peritoneal implants including diaphragmatic implants is facilitated by the use of Cavitron ultrasonic surgical aspirator (CUSA) and argon beam laser. Other modalities used are carbon dioxide laser and loop electrosurgical excision procedures^{5,6}. However in best hands and best centers, many times the initial laparotomy turns out to be non therapeutic. The mortality and the morbidity due to haemorrhage in the presence of friable growth may be overwhelming. In order to circumvent this problem and in view of the excellent response of tumor observed even after the futile initial laparotomy, the concept of interval laparotomy has come into practice.

There is no randomized trial data published in favour of interval cytoreduction. However several phase II and retrospective data showed 3-year survival rate of 50%, which is comparable to optimal primary debulking. With neoadjuvant chemotherapy (NAC) 50% complete remission rate is reported and the complete / optimal resection is possible in 75% of cases. Our own data shows that the rate of optimal cytoreduction is 50% for primary surgery and 88.6% for patients who received NAC⁷. However it has to be clear that good reduction is not equivalent to initial small volume disease.

For interval debulking also, just like primary surgery, one has to be prepared for any extent of surgery to completely remove the disease to microscopic level. So the minimum prerequisites for an ovarian cancer laparotomy are adequate infrastructure with adequate theatre facilities, dedicated team with adequate expertise and oncology concept. It has to be ascertained that no facility should offer surgery for patients with ovarian cancer if adequate standards of care cannot be met with.

Meticulous and systematic pre-operative evaluation has to be done to assess the operability and to avoid a non-therapeutic laparotomy.

THE PREDICTORS OF SURGICAL OUTCOME ARE:

1. Clinical evaluation: age above 50 years, gross ascites and fixed large pelvic masses are unfavourable clinical factors.

2. Abdominal ultrasound: large volume ascites and hydroureteronephrosis increase the inoperability rates.
3. CT scan: Bristow 2000 selected 13 radiographic features along with performance status⁸. The important radiographic criteria considered are number of metastasis, peritoneal thickening, large ascites, large metastatic deposits on diaphragm, suprarenal nodes, etc. Each parameter was assigned a numerical value. They reported that with a predictive index > 4, the specificity was 85% (inappropriate unexploration 15%) and the sensitivity approached 100% (unnecessary exploration 0%). According to Dowdy, diffuse peritoneal thickening and large volume ascites independently predicted surgical outcome.
4. Diagnostic laparoscopy:

Inoperability criteria in advanced ovarian cancer:-

Absolute	
a.	Stage 1V disease or
b.	Metastasis of more than 1 cm at sites where optimal cytoreduction is not possible, e.g. at porta hepatis, around superior mesenteric artery, etc.
Relative	
a.	Uncountable (100) peritoneal metastases
b.	Estimated total metastatic load of > 1000gm (both intra and extraperitoneal)
c.	Presence of more than 10gms peritoneal metastatic plaques
d.	Large volume ascites (5L)
e.	Those with performance status 2 or 3

The time interval between diagnostic laparoscopy and definitive surgery or chemotherapy should be as short as possible.

ROLE OF RETROPERITONEAL LYMPH NODE DISSECTION (RPLND)

Lymph nodal involvement in ovarian cancer is 20-40% (40 JSO) in apparently early disease to as high as 70-80% in advanced disease. Early stages LND is recommended as a part of staging (some studies show improved survival also) and in advanced disease involved nodes are removed to attain R0 – R1 status.

ROLE OF HYSTERECTOMY

No studies so far tested the benefit of uninvolved uterus⁹. However, uterus should not be removed in instances of suboptimal tumor removal, since in the event of a subsequent recurrence, the tumor will directly invade the bladder.

CURRENT CONCEPTS IN BORDERLINE SEROUS TUMORS

Invasive serous carcinoma of ovary is divided into low-grade and high-grade tumors by the 2-tier system of grading designed by the M D Anderson Cancer Center (2004). The term microinvasive serous carcinoma was coined by John Hopkins University and is subclassified into noninvasive and invasive. Currently, non-invasive micropapillary tumor is considered as a variant of serous tumor of low malignant potential (STLMP) and invasive is synonymous with low-grade serous tumour (LGSC)¹⁰.

Data suggests that STLMP and LGSC share a common pathogenesis whereas the high-grade serous carcinoma (HGSC) has a distinct and different pathogenesis.

MOLECULAR EVIDENCE

K-ras and BRAF mutations are detected in 1/3 of STLMP and LGSC and are mutually exclusive. A k-ras mutation seen in STLMP is rare in HGSC and the BRAF mutation is non-existent. CHEK2 is a protein kinase that is involved in cell cycle arrest. Genotyping revealed a strong positive association between the CHEK2 1157T missense variant and ovarian cystadenomas, STLMP and LGSC. Such association is not found in HGSC. On the other hand p53 mutation occur frequently in HGSC, but rarely seen in STLMP and LGSC.

CLINICAL EVIDENCE

30% of STLMP is associated with implants, more common in micropapillary type. In 70-80% of patients with STLMP who relapse, the histology of recurrence is LGSC.

It is a great dilemma for the gynecologic oncologist whether to do a restaging, when a patient with STLMP is referred after removal of only the primary tumor. This is a controversial point; current recommendation is to go for a comprehensive counselling for restaging versus surveillance^{11,12}. But a concomitant surgical staging along with primary tumor removal would be preferable in ideal circumstances. This can assess the prognosis and obviate the need for restaging if it turns out to be invasive carcinoma on final paraffin sections.

CHEMOTHERAPY OF EPITHELIAL OVARIAN CANCER (EOC)

Early stage disease:

Early stage disease is classified as low-risk or high-risk, based on prognostic factors. Low-risk are patients with stage 1A/1B, grade 1 with non-clear cell histology. This group has a 5-year survival rate of more than 90% and can be left alone without any adjuvant treatment.

High-risk factors are stage 1C/11, grade 2 & 3, clear cell histology and dense adhesions. High-risk patients have a relapse rate of about 40-50 % and warrants adjuvant treatment. Paclitaxel and carboplatin combination given every 3-4 weeks for 6 cycles is the standard practice at this time.

CHEMOTHERAPY OF ADVANCED EOC

Consensus exists as to the use of platinum based chemotherapy in this situation. Though controversies exist with regard to which platinum, which taxane, whether anthracycline is to be added or not, etc., the standard practice at present is 6 cycles of paclitaxel (175mg/m² over 3 hours) and carboplatin (AUC 6)

CHEMOTHERAPY IN RELAPSED OVARIAN CANCER

Treatment options depend on whether it is a platinum sensitive relapse (platinum free interval more than 6 months) or a platinum resistant/refractory relapse. Platinum sensitive patients can still respond to platinum based chemotherapy combinations. Judicious use of drugs to balance the potential benefits, toxicity and patient acceptance need emphasis in the treatment of relapsed ovarian carcinoma. Though most of the drugs claim a response rate of 20-30%, liposomal doxorubicin stands as one of the preferred options in the treatment of relapsed EOC. Topotecan, docetaxel, gemcitabine, oral etoposide / altretamine are the most commonly used other second line drugs.

THE FUTURE

Targeted and tailored therapy is likely to play an important role in the management of EOC in the future. Blockage of epidermal growth factor pathways with Erlotinib, use of antiangiogenesis drugs like bevacizumab etc. is gaining momentum. Conventional drugs like paclitaxel used as weekly schedule was found to be well-tolerated and active in patients with platinum resistant disease, opening up innovative ways of administering currently available conventional drugs.

CONCLUSION

Surgery and chemotherapy play important role in the management of ovarian carcinoma.

Upfront surgery/chemotherapy is decided mainly on clinical judgement and CT criterias. Currently, there is limited role for laparoscopy in the management of ovarian tumors. Lack of adequate sensitivity and specificity of currently used methods curtail early detection, so prevention with preservation of ovaries needs further studies. Tailored and targeted therapy can replace the current standard of care in future.

REFERENCES

1. Kauf ND, Satagopan JM, Robson ME, et al. Risk reducing salpingo-oophorectomy in woman with a BRCA1 or BRCA2 mutation. *N Eng J Med* 2002;346:609.
 2. Grann VR, Jacobson JS, Thomason D, et al. Effect of prevention strategies on survival and quality adjusted survival of women with BRCA1/2 mutations; an updated decision analysis. *J Clin Oncol* 2002;20:2520.
 3. Eisenkop SM, Nalick RM, Wang SJ, et al. peritoneal implant elimination during cytoreductive surgery for ovarian cancer: impact on survival. *Gynecol Oncol* 1993;51:224-9.
 4. Podratz KC, Aletti G, Cliby WA. Advanced ovarian cancer surgical management: *Indian J of Gynecol Oncol* 2006; 6 suppl 1:11-2.
 5. Patsner B. Carbon dioxide laser vaporization of diaphragmatic metastases for cytoreduction of ovarian epithelial tumor. *Gynecol Oncol* 1990;76:724-7.
 6. Fanning J, Hilgers RD. Loop electrosurgical excision procedure for intensified cytoreduction of ovarian cancer. *Gynecol Oncol* 1995;57:188-90.
 7. Sharma S, Vijayakumar K, Chitrathara K, et al. Neoadjuvant chemotherapy in advanced epithelial ovarian cancer: a retrospective study. *Indian J of Medical and Paediatric Oncology* 2007;28 No 1:7-13.
 8. Bristow RE, Duska LR, Lambrou NC, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. *Cancer* 2000;89:1532-40.
 9. Munstedt K, Franke FE. Role of primary surgery in advanced ovarian cancer. Review. *World J of Surgical Oncology* 2004;2:32.
 10. Burks R, Sherman M, Kurman R. Micropapillary serous carcinoma of the ovary. A distinctive low-grade carcinoma related to serous borderline tumors. *Am J Surg Pathol* 1996;20:1319-30.
 11. Lin PS, Gershenson DM, Bevers MW, et al. The current status of surgical staging of ovarian serous borderline tumors. *Cancer* 1999 Feb 15;85(4):905-11.
 12. Fauvet R, Boccaro J, Dufournet C, et al. Restaging surgery for women with borderline ovarian tumors: results of a French multicenter study. *Cancer* 2004 Mar 15;100(6):1145-51.
-

Comprehensive Rehabilitation: A New Dawn for the Disabled

J.N. Panicker

CASE VIGNETTE

A previously healthy 25 year-old manual worker, the sole breadwinner of a family, falls from the third floor of a building at a construction site. Luckily, other than being a bit dazed, he has not suffered any head injuries. But he has severe back pain and is unable to move his legs. His lower limbs are flaccid and weak and he has a sensory level at the 12th thoracic dermatome with loss of all sensations below. He has tenderness at the 9th thoracic vertebra and also retention of urine. X-ray and subsequently MRI confirm the fears of a fracture, showing burst fracture of the 9th thoracic vertebra and spinal cord transection. He undergoes intensive therapy and surgery for fracture site stabilization. Active management is complete and he is now awaiting discharge- as a paraplegic.

“WHAT NEXT?”

During the initial days following a medical or surgical condition, patients are actively managed and regularly briefed by treating doctors. Patients tend to assume that total cure is certain and will happen in the immediate future. However many times, at the time of discharge, they find themselves to be *stabilized* at a level of functioning that is far from the state of “normalcy” and “cure” that they had assumed. Unmet expectations lead to frustrations and patients start asking questions- “What next?”, “Where do I go for help now?” or “Who will help me?”. With time, the questions become more broad-

“How do I face my people?”, “Will I be able to work?” or “Who will look after my family?”. Most of the time, the treating team of doctors has no concrete answers to these relevant yet complex questions. It is at this critical juncture that a comprehensive rehabilitation team should take over.

REHABILITATION: STARTING THE PROCESS

Rehabilitation is the active participation of the disabled person and others to reduce the impact of disease and disability on daily life. It is a creative process by which all possible means are utilized to reduce the impact of disease by optimizing and maximizing social participation. By this process, a *disabled* person is made into a *differently abled* person. Importantly, it is the third stage of

medical care after prevention and cure. Any patient who is left with disabilities following a medical or surgical ailment is a potential candidate for entering a rehabilitation programme that is specific for his needs.

The first step in rehabilitation is to identify the problems being faced by a patient which are consequent to his illness. This includes defining the dimensions of disablement. **Impairment** is the loss or abnormality of anatomical, physiological or psychological structure or function. **Disability**, which results from impairment, is the restriction or lack of ability to perform an activity in the manner or range considered normal. **Handicap** is the disadvantage for a given individual in his social context, resulting from an impairment or disability, which lim-

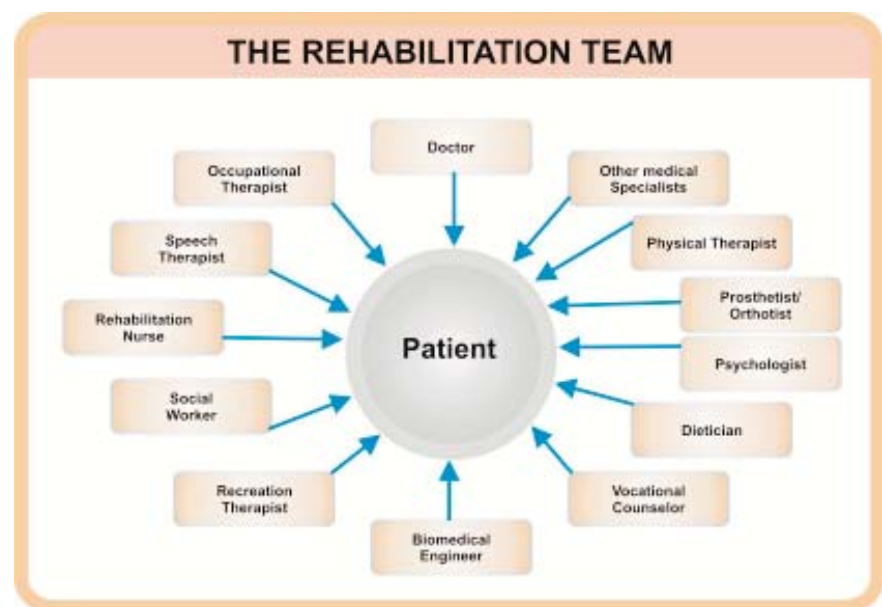


Fig. 1: The Rehabilitation Team

its or prevents the fulfillment of a role or participation in society that is considered normal (International Classification of Impairments Disabilities and Handicap, WHO 1980). In the patient described in the case vignette, paraplegia and inability to pass urine are examples of impairment, difficulty to walk is his disability and inability to look after the family and earn a livelihood are likely to be his handicaps.

THE REHABILITATION TEAM

Rehabilitation relies upon several disciplines that work together and cohesively to achieve aims and goals. Team effort is essential and the only criterion for becoming a member of the team is interest in contributing to the medicosocial rehabilitation of the patient. All team members are equal in position and the patient is the central figure (Fig.1). In institutional based rehabilitation, the members of the multidisciplinary team include:

1. **Doctor** plays many roles in rehabilitation (Table 1). Doctors on the team may include the original treating physician such as neurologist, neurosurgeon, internist, pediatrician, geriatrician, orthopedic surgeon or plastic surgeon, who may be interested in continuing to care for the patient during the rehabilitation phase of treatment, and/or physiatrists, who have specialization in rehabilitation. In a multidisciplinary team, the doctor is generally the team leader and his most important function is perhaps to coordinate the entire rehabilitation efforts to ensure smooth and goal-directed progress.
2. **Physical therapist** is responsible for strengthening muscle power, improving range of joint movements and reducing spasticity through a variety of exercises. He also plays an important role in training patients to improve sitting and standing balance, gait and transfers from bed. He may use various physical modalities such as heat, cold, electrical stimulation, LASER and massage for pain relief. Pool based therapies (hydrotherapy) facilitates many of the functions of the therapist.
3. **Occupational therapist** trains patients in maximizing self-care activities such as dressing, bathing, toilet and eating. He also trains patients to transfer from the bed, improve hand functions and explore various vocational skills. He evaluates the home of the patient and suggests modifications to make it barrier-free to facilitate movement of the disabled. He can advice regarding proper wheelchair prescription and also in driving skills.
4. **Prosthetist/Orthotist** is responsible for designing, fabricating and fitting orthoses (caliper, splint) and prostheses (artificial limb).

Table 1: Role of the Doctor in Rehabilitation

1.	Clinical Assessment and Confirmation of the diagnosis
2.	Identification of the medical, surgical and rehabilitation-specific problems faced by the patient
3.	Evaluation of the extent and severity of disabilities
4.	Goal setting
5.	Liaison between various team members to facilitate a coordinated effort
6.	Planning physical, occupational therapy and types of calipers/splints
7.	Planning and carrying out relevant investigations: electrophysiology, radiology, urodynamic studies
8.	Medical management of spasticity, urinary bladder/bowel/sexual dysfunction, seizures, pain
9.	Planning specific measures for spasticity management such as botulinum toxin injections and baclofen pump implantation
10.	Surgical correction of deformities
11.	Liaison with other medical and surgical specialists

5. **Psychologist** plays a crucial role in assessing personality and behavioural problems that may impede the rehabilitation process. In brain-injured patients, he conducts detailed assessment of cognitive functions and can plan a formal cognitive retraining programme. The psychologist also plays an important role in counseling patients and their caregivers.
6. **Speech therapist** assesses the types and severity of dysphonia, dysarthria and aphasia and plans a scientific speech therapy programme. In patients with little or no clear speech, augmentative and alternative communication (AAC) techniques can be taught to the patient to improve communication. Speech therapist also assesses swallowing dysfunction and carries out comprehensive programmes for improving swallowing.
7. **Social worker** often serves as the bridge between patients, caregiver and the rehabilitation team. He analyses the home environment and social support system into which the patient will go back after discharge. He facilitates the rehabilitation programme by tackling conflicts- both potential and real. He assesses the financial status and may suggest various vocations that the patient can learn according to his disabilities. He can also give guidance regarding welfare schemes of the government and various agencies.
8. **Vocational counselor** advises regarding employment and income generation for the rehabilitated patient. Vocations may include candle making, handicraft and woodwork, baking and computer-based jobs, paper bag making and operating telephone booths.
9. **Recreation therapist** uses recreational activities such as games, dramatics and picnics to improve group activities, social skills and tackle behavioural problems.
10. **Rehabilitation Nurse** forms the cornerstone of any rehabilitation ward and has special training in the long-term care of bed-bound patients, prevention and management of pressure ulcers and bowel/bladder incontinence. In some rehabilitation centres, specialized nurses may be available who focus only on pressure ulcer (tissue viability nurses) or bladder/bowel (continence advisors) management.
11. **Dietician**
The rehabilitation team would require occasional inputs from other specialists such as biomedical/rehabilitation engineers, neurologists, neurosurgeons,

orthopedic surgeons, urologists, gastroenterologists, pain and palliative specialists, obstetricians and gynecologists and plastic surgeons and they become part of the extended team.

GOAL SETTING: AN ESSENTIAL COMPONENT OF REHABILITATION

The success of a rehabilitation programme often lies in negotiating appropriate aims and goals that a given patient is expected to achieve. The **aim** of a rehabilitation programme is the overall outcome that the rehabilitation team and the patient expect to be achievable. It is decided upon by consensus. A rehabilitation programme that addresses all the problems of the patient is then planned and carried out by following a series of short-term **goals**. In a successful programme, the patient serially attains one goal after another and ultimately achieves the aim.

Before goals are set, several factors should be taken into consideration. These include age of the patient, comorbidities such as coronary artery disease or osteoarthritis that may limit activities, complications such as heterotopic ossification that may preclude active joint mobilization, and the expected overall outcome from the underlying disease. Of equal importance is the motivation of the patient and caregiver for active rehabilitation, dedication of the rehabilitation team and the infrastructural and financial resources available to execute the programme. The patient and caregivers play a paramount role in setting the goals of rehabilitation. The entire process is flexible and goals may be reset at any time during the programme according to needs or complications that may arise. Goal setting is both a science and art and it is useful to remember a few principles, known by the acronym S.M.A.R.T. Goals should be:

1. **Specific**
2. **Measurable**
3. **Achievable**
4. **Relevant to the rehabilitation aim**
5. **Timed: achievable within a defined period of time**

Once goals are set and a time frame is planned, members of the team start working with the patient. Patients are followed up using simple rating scales such as the Barthel Index for activities of daily living and Functional Independence Measure (FIM). The rehabilitation team meets regularly to review the progress of the patient.

The aims for the patient presented in the case vignette may be: ability to walk with assistance of bilateral knee ankle foot orthosis (calipers) using a walker (mobility aid) for short distances, and to achieve optimal urinary

bladder drainage. A sequence of short-term goals to be achieved over a 3 months period may be: strengthening of upper limb muscles, achieving independent sitting with support, then independent sitting without support, learning proper donning and doffing of calipers, learning to transfer from bed to chair and bed to standing position, standing with full support, then standing with support using a walker and finally mobilizing with the aid. To achieve optimal urinary bladder drainage, the goal may be to become proficient in self-drainage of urine by clean intermittent catheterization. Though the doctor, physio-therapist and occupational therapist may spend most time with the patient, other members of the team would be having important roles. The orthotist would design the knee ankle foot orthosis after taking measurements and would also follow up to ensure that it is fitting well. The social worker would focus on the support system available from the family and the construction company and also identify potential conflicts that may arise during rehabilitation. A home visit would be arranged during which the occupational therapist would assess any architectural barriers that may restrict movement with a walker and simple modifications would be suggested to make it barrier-free. The social worker and vocational counselor would discuss alternate sources of income generation. The patient would be taught clean intermittent self-catheterization by the physician and this would be monitored by the rehabilitation nurse. The dietician would plan a diet with optimal calorie intake. By the end of 3 months, he would be ready to reenter society with confidence and dignity, knowing well that he is independent for most of his requirements and would be able to look after the needs of the family.

DELIVERY OF REHABILITATION

The initial period of rehabilitation is based in institutions. It should be attached to a hospital so that patients may receive efficient management of medical complications. However it should ideally be physically separated from the hustle and bustle of the hospital to allow it to develop a separate identity. Subsequently, patients should be encouraged to return to society as earning members, retaining the optimal level of independence for activities of daily living that he achieved during rehabilitation. Community based rehabilitation should be encouraged in which members of society, in addition to the patient and care givers, take an active role in helping people with disability become socially reintegrated into the community.

REHABILITATION IN INDIA

India is a virgin ground for setting up a network for comprehensive rehabilitation. The strongly motivated family support system, which is still intact in India today, plays an important role in ensuring the success of a rehabilitation programme. Alternative systems of medicine such as Ayurveda and Yoga should be incorporated into the comprehensive rehabilitation programme and India should pioneer an evidence based programme involving judicious use of various systems of medicine for the overall management of patients. These factors may shorten the period of time required for achieving goals and will also improve patient satisfaction.

FUTURE TRENDS IN REHABILITATION

The explosive foray of computers and technology into all realms of society has pervaded the field of rehabilitation sciences as well. The future is bright for newer technologies such as assistive devices that facilitate use of computers by quadriplegics, environmental control units, novel wheelchairs and vehicle modifications. In the coming years, stem cell therapy, brain-computer interfaces, called neuroprostheses, bionic arm, microelectrode array based technologies and robotics will become part of the armamentarium of the rehabilitation team.

CONCLUSION

Comprehensive rehabilitation is essential to complete the package of medical care offered to patients. It is the responsibility of every health care worker to ensure that patients with residual disabilities be made aware of the potentials of rehabilitation so as to achieve optimal independence. They should be directed to a proper rehabilitation centre to continue care. The starting of multidisciplinary institutional based rehabilitation at Amrita Institute of Medical Sciences will go a long way in meeting this need.

REFERENCES

1. Greenwood RJ, Barnes MP, McMillan TM, Ward CD, editors. Handbook of Neurological Rehabilitation. Hove: Psychology Press; 2003.
2. Sunder S. Textbook of Rehabilitation. New Delhi: Jaypee Brothers; 2002.
3. Barnes MP. Principles of Neurological Rehabilitation. J Neurol Neurosurg Psychiatry 2003;74:3-7.

Caution! Counterfeit Medicines are on the Rise

B.P. Rao

ABSTRACT

Fraudulent medicines present a serious health and economic problem worldwide. Currently 6 to 10% of the global medicines trade is counterfeit. In India the figure may be around 20 to 25%. Obviously such drugs fail to meet the prescribed standards in safety, quality, and efficacy and fail to comply with the national and international laws related to Good Manufacturing and Trade Practices of Pharmaceutical Products. Over 50% are sold via E- trading. Lack of legislation, lack of enforcement, lack of anti-counterfeit culture, and lengthy court procedures are some of the perpetuating factors for counterfeiting pharmaceutical products. The trail from raw material to appearance on a pharmacy shelf involve as many as four countries and is well organized just as drug trafficking. International efforts are required to crack down the network of manufacture and sale of counterfeit medicines. International Medical Products Anti-Counterfeiting Taskforce (IMPACT) has been set up in the United States of America and many European countries. Development of Global Anti- Counterfeit Task Force is on the anvil. Pharmacovigilance programmes are extended to include reporting and investigating suspected cases of counterfeit drugs. Public awareness and political will are crucial factors in the fight against counterfeiting of medicines.

INTRODUCTION

Alarm bell is ringing. Listen! It is echoing "Caution! Counterfeit Medicines are on the Rise". It is estimated that 6 to 10% of the global medicines trade is counterfeit. Around 1% in Europe; 10-30% in parts of Asia, Africa and parts of Latin America; over 20% in former Soviet Republics. A global increase of more than 90% is expected by 2010.

According to estimate made by Associated Chambers of Commerce and Industry of India (Assoc hem) 20% of medicines sold in India are fake. That means one in every five medicines consumed by an Indian is likely to be a fake one. Over 50% of them are sold via the Internet trading. In India alone spurious medicines market has grown to Rs. 4,000 crores in 2006 as against Rs.3,000 crores in 2005.

THE RED ALERT AND THE ACTION PLANS

The red alert on counterfeit medicines was first sounded during the Conference of Experts on the Rational Use of Drugs, held in Nairobi in November 1985. In 1988, the Forty-first World Health Assembly adopted a resolution (WHA 41.16) requesting the Director- General "To initiate programmes for the prevention and detection of the export, import and smuggling of counterfeit medicines and requested governments and pharmaceutical firms to cooperate with the Secretary – General of the United Nations in cases when the provisions of the International Drug Treaties are violated".

Accordingly, in 1995 World Health Organization and pharmaceutical firms jointly formulated a global project to combat the menace of counterfeit drugs. They developed simple measures like inspection and cost effective methods of analysis of suspected samples and these are being promoted.

Evidence is emerging of unholy nexus between pharmaceutical counterfeiting and international narcotic lobbies. Recently, an "International Medical Products Anti-counterfeiting Taskforce (IMPACT)" has been established in the United States of America and in many European countries to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, spurious/ counterfeit or substandard pharmaceutical preparations and monitor cases of violation of the provisions of the International Drug Treaties.

DEFINITION

A counterfeit medicine is one, which is deliberately and fraudulently mislabelled with respect to its identity and / or source.

MEDICINES MAY BE CONSIDERED AS COUNTERFEITED:

1. Insufficient quantity of medicine(s)
2. Substandard ingredients

3. No medicine as labelled
4. Inappropriate, but harmless ingredient(s) in place of the labeled medicine(s)
5. Inappropriate as well as potentially harmful ingredient(s) in place of the labeled medicine(s)
6. Added - unlabeled harmless /potentially toxic /banned ingredients e.g., steroids with herbals
7. Expired medicines repacked and relabeled
8. Medicines mimicking the original product in package design and label (fake packaging of legally manufactured medicine)

THE POOR VICTIMS

The entire human population are aggrieved and their lives are at risk. Many case of fatalities and morbidity have been reported from India. Category wise consequences are given below:

1. **Consumers, the primary victims:**
 - May be innocuous
 - May result in permanent disability
 - May be fatal
2. **Legitimate manufacturers:**
 - Undermine the confidence in their product
 - Incur loss of sales
3. **Government:**
 - Fiscal loss of revenue to purchase spurious medicines
 - Lead to collapse of health sector
4. **Health care professionals:**
 - Loss of patient's confidence in their services
 - Loss of revenue

THE CONCERN

Initially counterfeiting was limited to comparatively expensive medicines. Today scenario has changed. Prescription, nonprescription, generic, branded, over-the-counter, life saving; all are being counterfeited.

Many cases of fatalities have been reported from India due to the use of counterfeit medicines.

FACILITATING FACTORS FOR COUNTERFEITING

1. High demand for medicines
2. High cost of medicines and price variation
3. Easy for transportation
4. Scarcity and erratic supply of basic medicines

5. Weak drug regulatory control in the fields of manufacture and marketing
6. Poor socioeconomic status of the population - easy prey to corruption
7. Lack of know how and lack of resources for quality assessment
8. Lack of public awareness and political will
9. Boost in the unscrupulous E- advertising and trading practices

STRATEGIES TO COUNTER THE MENACE OF COUNTERFEITING

1. At the International Level:

- a. World Trade Organization's General Agreement on Tariffs and Trade - Trade Related Aspects of Intellectual Property Rights Agreement 1994 (GATT -Trips Agreement 1994)

All types of Intellectual property rights like patents, copyright and trademarks are protected globally by GATT- TRIPS Agreement 1994 signed by all member countries of the World Trade Organisation (WTO). This agreement covers all areas of business and sociey like pharmaceceuticals, software, music, arts etc. The Agreement details all the rules related to enforcement of international laws in cases of fraud or counterfeiting like collection and documentation of evidence, provisional measures to be adopted in such cases, penalties to be meted out etc. It is further agreed that that courts should have the right, under certain conditions, to order the disposal or destruction of pirated or counterfeit goods.

- b. International Medical Products Anti-Counterfeiting Taskforce (IMPACT)

International Medical Products Anti-Counterfeiting Taskforce (IMPACT) has been set up in the United States of America and many European countries. Development of Global Anti- Counterfeit Task Force is on the anvil.
- c. Pharmacovigilance systems should be extended to include reporting of and investigating suspected cases of counterfeit medicines.
- d. Custom Offence
 1. **Treat willful Counterfeiting of trademark as criminal offence**
 2. **Enact and implement appropriate legislation to protect intellectual property right and to counter the movement of counterfeit and pirated goods across the border under the clause "custom offence"**

e. **Awareness**

Create awareness to the public about the existence of counterfeit pharmaceutical products and the related health hazards. This is necessary in order to mobilize the political will for effective implementation of counter measures.

2. At the National Level:

a. Legal administrative network: **Set up a legal administrative framework to define and control the legitimate drug market and the drug distribution system.**

b. **Quality assurance: Apart from licence for Product Manufacture and Marketing from the local authorities, certification on Good Manufacturing Practice (GMP) to be made mandatory. These steps help to ensure the quality of the products and to establish the sites of origin of the pharmaceutical product(s).**

c. **Quality Assessment:**

Provide easily identifiable, and interpretable markers of quality assessment ^a develop low technology, easy methods of quality assessment e.g. colorimetric assay.

d. **Rational Therapy and Rational Use of Drugs:**

Promote rational therapy and rational use of drugs and prepare or update Essential Drugs List.

e. **Price:**

Initiate measures to reduce the price of lifesaving medicines.

f. **Pharmacovigilance:**

Helps to identify substandard and fake medicines

Include pharmacovigilance in the medical and paramedical curriculum.

Design web sites to give safety alerts

without generating unwarranted public alarm.

g. **Education:**

Organize a programme of education on counterfeit medicines to community leaders, teachers, media, police, traditional healers, and local healthcare professionals.

h. **Punishment:**

Consider counterfeiting as an explicit criminal offence liable for punishment.

3. At the Pharmaceutical Industries Level:

Pharmaceutical firms very often do not publicize the problem because they are afraid that the existing market may be lost. Sometimes the loss of revenue may be up to 30%.

a. **Quality Assurance:**

Assure quality of raw materials as well as finished products

Follow WHO Guidelines on Good Manufacturing Practices in the processes of procurement of raw materials, and manufacture of medicines.

b. **Protection from tampering:**

Use tamper resistant and tamper evident holograms, colour shifting inks, water marks, tapes etc to authenticate the package and the product.

c. **Good trading practices:**

Follow legal Good Trading Practices in the distribution and marketing of medicines.

Avoid distribution of products through a large number of intermediaries and complex transactions.

1. **Certification on Good Manufacturing Practice (GMP) should be made mandatory.**

2. **Promote rational therapy and rational use of drugs and prepare or update Essential Drugs List**

4. At the Wholesaler Level:

1. **Direct Route:**

A legitimate role exists for the responsible wholesaler to see that the product reaches the end-user by the most direct route that is practicable.

2. **Registration:**

Each facility within the distribution chain must be registered, licensed, inspected and required to maintain complete records of the source from which consignments are purchased.

3. **Records:**

To facilitate the investigation of suspected counterfeit products and their origin, maintenance of acquisition and sale records is very important.

4. **Number of Transactions:**

There should not normally be more transactions between the wholesaler and dispensing pharmacist than between the manufacturer and wholesaler.

5. **Pharmacist:**

As a condition of licensing, distributor should employ a suitably qualified person, preferably a pharmacist, to be responsible for documentation and quality assessment of the products purchased.

5. At The Pharmacist Level:

The Professional bodies of Pharmacists have a high responsibility.

Purchase and sale:

The Professional bodies of pharmacists should exhort pharmacists:

To purchase stocks from sources reputed for integrity.

Not to purchase and sell suspicious products.

To report any suspicion on spurious / counterfeit products to the authorities/ pharmacovigilance cell in the area.

To fully cooperate with enforcement agencies.

a. **Communication:**

The Professional bodies should maintain effective channels for communication with enforcement agencies and legitimate manufacturers.

b. **Education:**

The Professional bodies should take the initiative in consumer and public education spread information on suspected counterfeiting activity to their members.

They should devise and disseminate simple safety tips for the consumers.

6. At the Consumer Level:

Consumers are advised to be particularly vigilant about their medications.

These products may be expired, contain incorrect ingredients or amounts of active ingredients, or be enclosed in packaging that does not match the product inside.

Consumers are advised to be particularly vigilant about their medications.

SIMPLE SAFETY TIPS FOR THE CONSUMERS

1. Look at Your Medicine:

It is very difficult for healthcare professional, let alone the patient to identify a counterfeit product just by looking at a medication or its packaging.

a. Read the instructions **printed on the product, the package or the package insert.**

The label or the package insert should provide all the basic information about the product and the manufacturer. These are required for the safe and effective use of medicines.

b. **Signs of tampering**

Package / container is different, unduly soiled or damaged.

Contents show signs of decaying like discolouration, cracks, precipitate etc.

c. **Information about the product:**

Name of the product (generic and registered).

Strength.

Total quantity in a pack.

Unit dose, and dosage per day, dosage interval.

Route of administration.

Synopsis on pharmacology.

Warnings, interactions - possible drug - food and drug – drug interactions.

d. **Information about the manufacturer:**

Name of the manufacturer /distributor.

Licence number of the manufacturing firm and / or distributor.

Lack of basic information about the product in question or an unprofessionally prepared document with factual errors and /or spelling and grammar mistakes should arouse suspicion of a spurious medicine.

2. Talk To Your Pharmacist:

If the package is different or damaged.

If there is variation in shape, colour, consistency, taste, smell, or feel.

If it does not produce the expected results or it produces. This can be due a number of reasons, including:

- a. Your body's response has changed over time (requiring a higher or lower dose).
- b. You have a new medical condition that changes the medication's effectiveness, or
- c. An interaction has occurred among medications, vitamins, or herbal supplements you are taking or specific foods you are eating
- d. you have received a counterfeit medicine.

If it produces unusual experiences

It may be due to side effects, interactions or allergy.

3. Advice on Procurement of Medicines:

a. **Authorised dealer**

Chances of getting original medicines are high when medicines are purchased from reputed, known, authorized pharmacies.

b. **Beware of E- trading**

Consumers are advised not to be lured by the advertisements that appear in the Internet. It is very difficult for the public to know whether the site is approved for E- trading or not. To stay safe, if medicine is to be purchased through e- trading outlet, chose a web site that posts the National Association of Boards of Pharmacies VIPPS (Verified Internet Pharmacy Practice Sites) symbol if such a system exists.

c. **Receipt**

Always demand bill after purchase. Verify whether batch number and expiry date are noted down on the bill.

1. Consumers are advised not to be lured by the advertisements that appear in the Internet.
2. Chances of getting original medicines are high when medicines are purchased from reputed, known, authorized pharmacies.
3. **Always demand for bill on purchase**

SUMMARY

No doubt, counterfeit medicines are a threat to very human existence. We have reached a stage where we are not sure whether the glucostrip we carry for self estimation blood glucose level is genuine or not, the vaccine we carry to protect the precious neonate is genuine or not or the antibiotic which we carry for our beloved is genuine or not. It is estimated that 10% of the medicines in the global market are counterfeits. Global eradication of counterfeiting should be the goal, a very difficult task to achieve. Counterfeiting should be considered as organized crime with deep rooted international links.

International trade regulations, effective utilization of Government machinery for making legislation and implementation, active involvement of Pharmaceutical industries and health professionals and more important consumer participation etc are absolutely essential to achieve partial success at least to contain the global problem of counterfeiting.

REFERENCES

1. Uppsala Reports January 2007.
2. The Hindu: Kerala: Economy / Business Saturday, 13 January 2007.
3. Goodman and Gilman's The Pharmacological Basis of Therapeutics eleventh Edition 2006.
4. Clinical Pharmacology 9th Edition P.N. Bennet and M.J. brown 2003.
5. Drug and Therapeutic Committees A practical Guide 2003.
6. Quality Assurance of Phramaceuticals volume 1. World Health Organization Geneva 1997.

Analysis of GSTM1 and CYP1A1 Genes in Tropical Chronic Pancreatitis: A Pilot Study

A.G. Unnikrishnan*, S. Ramachandran**, M.R. Pillai***, H. Kumar*, P. Nair****, R.V. Jayakumar*, U. Guruprasad*, R. Nandakumar****, T. Joseph**, I. Hariharan**, V. Balakrishnan****

ABSTRACT

Background/Objective The etiopathogenesis of tropical chronic pancreatitis (TCP) remains unknown. Oxidative stress and exposure to environmental toxins (xenobiotics) have been proposed as risk modifiers. The objective was to study the prevalence of selected abnormalities in the xenobiotic metabolizing genes in subjects with TCP.

METHODS

Twenty-one patients attending the Pancreas Clinic at our center were studied and the results of gene analysis were compared with a control group of 400 healthy volunteers. The outcome studied was the prevalence of deletions and mutations in the xenobiotic-metabolizing genes GSTM1 and CYP1A1 and the DNA repair gene XRCC1 in subjects with TCP.

RESULTS

Our results show that 9.5% of subjects with TCP had deletions of GSTM1 and 33% had polymorphisms of CYP1A1. In the control group (n = 400) the prevalence of these polymorphisms were 28% and 16% respectively. Compared with controls, polymorphisms of CYP1A1 were commoner in subjects with TCP, though this was not statistically significant (p = 0.064). The prevalence of GSTM1 polymorphisms was higher in the control group, but this too was not statistically significant (p = 0.077).

CONCLUSIONS

These results of this small pilot study do not imply that a genetic susceptibility to environmental disruptors could be an important factor in the pathogenesis of TCP. Larger studies are needed to assess the links between these genes and TCP, especially considering that both are associated with a higher risk of pancreatic cancer.

Keywords

Endocrine disruption, pancreatic diabetes, oxidative stress, xenobiotic, chronic pancreatitis, pancreatic cancer

ACKNOWLEDGEMENT:

We thank Surya Ramachandran and Indhu Hariharan for help in carrying out the analysis.

INTRODUCTION

The etiopathogenesis of Tropical chronic pancreatitis (TCP) has been a mystery^{1,2}. Malnutrition and cassava intake had been the preferred hypotheses earlier, but these hypotheses have now been strongly questioned^{3,4}. In recent times, genetic factors have led to a paradigm shift in the understanding of the illness⁵, TCP is increasingly being recognized as a heterogeneous disease with multiple risk factors^{3,5}.

These risk factors could either be an extrinsic toxin, or an intrinsic abnormality increasing the subjects' vulnerability to extrinsic factors.

Xenobiotics (environmental toxins like cigarette smoke and occupational chemicals) have been proposed as extrinsic factors involved in pancreatitis⁶. Xenobiotic compounds include solvents, fuels, phenols, polyaromatic hydrocarbons, herbicides, and halogenated alkanes. However their mere presence in the atmosphere is not sufficient, and increased susceptibility to these xenobiotics, it has been postulated, could be conferred by micronutrient deficiency and oxidant stress⁷. Stud-

ies on the anti-oxidant status of subjects with TCP have shown abnormal antioxidant status in these subjects^{7,8}. Micronutrient antioxidants react with glutathione that is present in tissues to accelerate disposal of reactive oxygen species as well as xenobiotic metabolites that may be derived via the cytochromes P450 pathway⁷. Pancreatitis can be caused by the heightening of oxidative-detoxification reactions induced by cytochrome p450-1 activity in the liver or pancreas. Theophylline clearance, which is a marker of cytochrome p450-1 activity in vivo, has already been shown to be increased in subjects with TCP⁹.

*Dept. of Endocrinology and Diabetes, AIMS, Kochi.

**Regional Cancer Center, Trivandrum.

***Rajiv Gandhi Center for Biotechnology, Trivandrum.

****Dept. of Gastroenterology, AIMS, Kochi.

Therefore, we postulated that genetic defects that increase the damage caused by environmental disruptors could play a role in the genesis of TCP. We studied the role of 2 genes important in the susceptibility and recovery from xenobiotic-induced oxidative stress. The two i.e. GSTM1 and CYP1A1 are important in oxidative-detoxification of environmental toxins and have already been implicated in the pathogenesis of pancreatitis⁶. This study was carried out in the state of Kerala in India, which is the region with one of the highest prevalence rates of subjects with TCP in the world¹⁰. In general, pesticide-related illness has been reported from Kerala¹¹.

METHODS

We studied 21 patients with tropical chronic pancreatitis (TCP), based on the following criteria: (1) recurrent pain (2) large intraductal calculi, particularly in the head region; (3) ultrasonological and ERCP evidence of pan-

creatic calcification; (4) absence of any other etiological factors like alcoholism, etc; (5) diabetes mellitus (may or may not be present). After obtaining informed consent, EDTA blood samples were collected from 21 patients. Genomic DNA was isolated from peripheral blood leucocytes following standard protocols. The methodology used for genotype analysis of the *CYP1A1*, and *GSTM1* was Polymerase Chain Reaction (PCR) with specific primers, using well-described protocols used by the collaborating center in earlier studies (Table 1)¹²⁻¹⁴. We also carried out genotype analysis of these genes in 400 healthy control subjects derived from the healthy volunteers.

The Institutional Ethics Committee had cleared the study. The two groups (cases and controls) were compared using Fischer's Exact test to compare frequencies. Two-tailed P values less than 0.05 were considered statistically significant.

Table 1: Methodology used for PCR for GSTM1 and CYP1A1

GSTM1 Analysis	
<p>PCR was carried out in a total volume of 50 microliter containing 0.5-1.0 microgram of genomic DNA, 120 ng of each of the primers (forward & reverse) for GSTM1 and beta-globin (control gene), PCR buffer (1X) [50mM KCl, 10mM Tris-HCl (pH 9.0), 1.5mM MgCl₂ and 0.1% Triton X-100], 200 micromolar of each dNTP and 1.25 units of Taq DNA polymerase. Negative controls consisted of a similar reaction mixture with the template replaced with sterile water. Initial denaturation at 94 deg C for 5 min followed by 30 cycles of denaturation at 94 deg C for 30 sec, annealing at 64 deg C for 60 sec and extension at 72 deg C for 60 sec. A final extension was carried out at 72 deg C for 5 min.</p> <p>The presence of 232 bp (GSTM1) and 265bp (beta-globin) bands implies the presence of GSTM1 while the presence of only 265bp band implies GSTM1 deletion.</p>	
Primer sequence:	
<p>GSTM1: A: 5'- GAA CTC CCT GAA AAG CTA AAG C - 3' B: 5'- GTT GGG CTC AAA TAT ACG GTG G-3' Beta-globin: C: 5'- CAA CTT CAT CCA CGT TCA CC-3' D: 5'- GAA GAG CCA AGG ACA GGT AC-3'</p>	
CYP1A1 m1 & m2	
<p>10 microliters of the purified PCR product was digested with 20 units of <i>MspI</i> (<i>CYP1A1 m1</i>) and <i>NcoI</i> (<i>CYP1A1 m2</i>) restriction enzymes at 37 degrees C for 1 hour. The RFLP products were then electrophoresed on an agarose gel and visualized using ethidium bromide staining. 100bp DNA molecular weight marker was used to assess the size of the PCR-RFLP products.</p>	
Evaluation of RFLP:	
<i>MspI</i> (<i>CYP1A1m1</i>)	<p>200 & 140bp=> homozygous variant 340, 200 & 140 bp=> heterozygous variant. 340 bp=> wild type</p>
<i>NcoI</i> (<i>CYP1A1m2</i>)	<p>232 bp=> wild type 232 & 263 bp=> heterozygous variant. 263 bp=> homozygous variant</p>

RESULTS

The mean age of the subjects was 43.4 +/- 12 years. Seven among the 21 subjects were females and 14 were males. Eleven subjects were of a lower socioeconomic status, while 10 subjects were of a middle-income socioeconomic status. Six out of the 21 subjects gave a history of cassava intake. Four among the 21 were smokers. Two subjects with TCP had developed pancreatic cancer (Table 2).

The results of the genotype analyses are shown in Table 1. Deletions of the GSTM1 were found in two (9.5%) subjects. Seven (33%) subjects had polymorphisms in the CYP1A1 gene, of which one was of a homozygous type, the rest being heterozygous. In a series of 400 blood samples obtained from healthy volunteers who have had no incidence of cancer or any other known systemic disease, we genotyped CYP1A1 and GSTM1 genes. The GSTM1 gene was deleted in 28% (n = 112/400) of the normal population and actively

present in 72%. For the CYP 1A1 gene 16% (n = 64) of the 400 normal population were polymorphic, of which 2% were homozygous polymorphic and 14% were heterozygous polymorphic. As compared with the control population, the prevalence of CYP1A1 polymorphisms was higher in the subjects with TCP (NS; $p = 0.064$; CI = 95%), but this did not reach statistical significance. The difference in the prevalence of GSTM1 too was not statistically significant when subjects with TCP were compared with healthy controls. ($p = 0.077$). Overall, 7 out of the 21 subjects (33%) had an abnormality in either the CYP1A1, or GSTM1 or both.

DISCUSSION

The results of this small study suggest that environment-disrupting genes are present in about one third of subjects with TCP. However, there was no statistically significant difference when compared with a control population. Hence our results largely negate, but do not completely rule out the effects of these functionally rel-

Table 2

Case no.	Remarks	GST M1	CYP 1A1
1	56 year male	PRESENT	WILD
2	15 year old girl With diabetes	PRESENT	WILD
3	30 year old male	DELETED	HETEROZYGOUS POLYMORPHIC
4	65 year old lady With diabetes	PRESENT	WILD
5	30 year old male Takes Cassava	PRESENT	WILD
6	42 year old male With Diabetes Takes Cassava Smoker	PRESENT	WILD
7	52 year old lady With Diabetes, Takes Cassava	PRESENT	HETEROZYGOUS POLYMORPHIC
8	53 year old male With Diabetes Takes Cassava	PRESENT	WILD
9	23 year old lady Severe Pain, Required Stenting	PRESENT	WILD
10	23 year old lady Obstructive Jaundice	PRESENT	WILD
11	67 year old male	PRESENT	WILD
12	36 year old male Pancreaticojejunostomy For Recurrent Pain	PRESENT	HETEROZYGOUS POLYMORPHIC
13	31 year old male	PRESENT	HETEROZYGOUS POLYMORPHIC
14	51 year old male With Diabetes Smoker	PRESENT	WILD
15	51 year old male With pancreatic cancer	PRESENT	WILD
16	42 year old lady With Diabetes	PRESENT	WILD
17	56 year old lady With Diabetes	DELETED	WILD
18	51 year old male With pancreatic cancer Smoker	PRESENT	WILD
19	39 year old male With diabetes Takes Cassava	PRESENT	HETEROZYGOUS POLYMORPHIC
20	19 year old male	PRESENT	HETEROZYGOUS POLYMORPHIC
21	47 year old male Smoker, Takes Cassava	PRESENT	HOMOZYGOUS POLYMORPHIC

evant polymorphisms in *low* penetrance genes. It is possible that these genes might cause additive or even synergistic effects on an individual who already has other risk factors for TCP. This fits in well with the current model of TCP as a heterogeneous, multifactorial disorder^{15,16}. Our study is limited by the small sample size, which prevents us from making statistically significant conclusions. The small sample size also meant that correlations between the genotype and phenotype would not be possible.

The *glutathione S-transferases* (GSTs) are a family of enzymes that help in detoxifying a wide range of chemicals and thus protecting the body from oxidative stress, including carcinogens. In some *GST* genes there are polymorphisms, which alter the activity of these enzymes. *GSTM1* genes exhibit deletion polymorphisms. Homozygous deletions of those genes, called *GSTM1* null genotypes, result in a lack of enzyme activity. A decrease in GST enzyme activity could result in inefficient detoxification of various carcinogens, which could lead to genetic

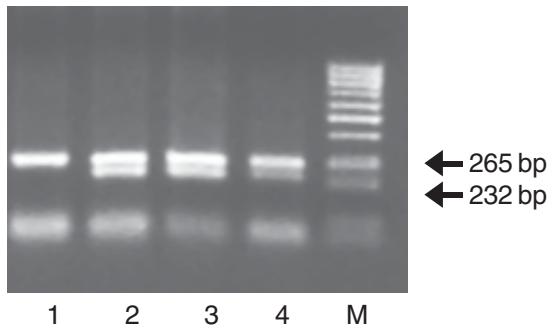


Fig. 1: Ethidium bromide stained agarose gel showing PCR products corresponding to the alleles of the *GSTM1* gene. "M" is the DNA Size marker. Lanes 2, 3 and 4 show presence of the *GSTM1* gene, and Lane 1 shows deletion of the gene.

damage and increased cancer risk¹⁷. GSTs have already been linked to pancreatic cancer¹⁸. In our study, the *GSTM1* deletions were present in only about 10% of the subjects, lower than the value of 28% in controls; this suggests that *GSTM1* does not appear to be an important gene in this setting of TCP. *GSTM1* has been linked to chronic alcoholic pancreatitis⁶. In a recent study, it was

shown that *GSTM1* is not involved in the pathogenesis of hereditary pancreatitis¹⁹. The role of *GSTM1* null mutations in chronic pancreatitis is controversial, and indeed, whether they protect or predispose to injury itself is a subject of debate^{20,21}.

One of the most interesting outcomes of this study was the increased incidence (though not statistically significant) of polymorphisms in the *CYP 1A1* gene.

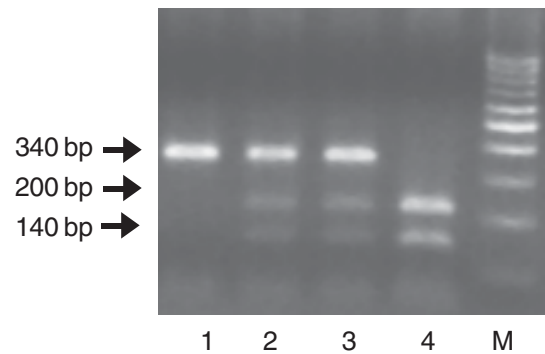


Fig. 2: Ethidium bromide stained agarose gel showing PCR products corresponding to the alleles of the *CYP1A1m1* genes. Lane 1 shows the wild type, lanes 2 and 3 show a heterozygous polymorphism, while lane 4 shows a homozygous polymorphism

Polycyclic aromatic hydrocarbons (PAHs), a class of chemicals that includes potent carcinogens, have been postulated to have a role in the genesis of TCP³. Automobile exhaust, industrial emissions and smoke from burning wood, charcoal and tobacco contain high levels of PAHs. The major metabolic pathway for ingested or inhaled PAHs to water-soluble derivatives is oxidative activation by *CYP1A1* followed by detoxification by phase II enzymes. If these are not removed from the body by this system, PAHs and their metabolites cause genetic and tissue damage²². Most environmental carcinogens undergo initial metabolism by CYPs (Phase I enzymes) into either inactive metabolites or into chemically reactive electrophilic metabolites which can bind to DNA and trigger a carcinogenic response; these reactive metabolites may be converted by both Phase I enzymes or by Phase II enzymes (e.g. GST) into inert, and biologically inactive products²³. Very recent studies of *CYP1A2* genes have shown that they could be an important factor in the pathogenesis of pancreatic cancer²⁴. In the only Indian

study looking into this aspect, theophylline kinetics, a marker for the potentially toxic CYP-450I pathway of drug metabolism, was studied in 11 controls and 11 patients with TCP: the results showed that theophylline clearance was faster among subjects with TCP, suggesting that the toxic pathways were activated⁹.

REFERENCES

- Mohan V, Premalatha G, Pitchumoni C. Tropical chronic pancreatitis: an update. *J Clin Gastroenterol* 2003;36:337-46.
- Chari S, Mohan V, Jayanthi V, et al. Comparative study of the clinical profiles of alcoholic chronic pancreatitis and tropical chronic pancreatitis in Tamil Nadu, south India. *Pancreas* 1992;7:52-8.
- Barman KK, Premalatha G, Mohan V. Tropical chronic pancreatitis. *Postgrad Med J* 2003;79:606-15.
- Mathangi D, Deepa R, Mohan V, et al. Long-term ingestion of cassava (tapioca) does not produce diabetes or pancreatitis in the rat model. *Int J Pancreatol* 2000;27:203-8.
- Chandak GR, Idris MM, Reddy DN, et al. Mutations in the pancreatic secretory trypsin inhibitor gene (PSTI/SPINK1) rather than the cationic trypsinogen gene (PRSS1) are significantly associated with tropical calcific pancreatitis. *J Med Genet* 2002;39:347-51.
- Burim RV, Canalle R, Takahashi CS, et al. Polymorphisms in glutathione S-transferases GSTM1, GSTT1 and GSTP1 and cytochromes P450 CYP2E1 and CYP1A1 and susceptibility to cirrhosis or pancreatitis in alcoholics. *Mutagenesis* 2004;19:291-8.
- Braganza J, Schofield D, Snehalatha C, et al. Micronutrient antioxidant status in tropical compared with temperate-zone chronic pancreatitis. *Scand J Gastroenterol* 1993;28:1098-104.
- Segal I, Sharer N, Kay P, et al. Iron, accurate and copper status of Soutwestern Blacks with calcific chronic pancreatitis. *QJM* 1996;89:45-53.
- Chaloner C, Sandle L, Mohan V, et al. Evidence for induction of cytochrome P-450I in patients with tropical chronic pancreatitis. *Int J Clin Pharmacol Ther Toxicol* 1990; 28:235-40.
- Balaji L, Tandon R, Tandon B, et al. Prevalence and clinical features of chronic pancreatitis in southern India. *Int J Pancreatol* 1994;15:29-34.
- Anand A. Kerala pesticide tragedy. *Natl Med J India* 2001;14:123-4.
- Joseph T, Kusumakumary P, Chacko P, et al. Genetic polymorphism of CYP1A1, CYP2D6, GSTM1 and GSTT1 and susceptibility to acute lymphoblastic leukaemia in Indian children. *Pediatr Blood Cancer* 2004;43:560-7.
- Sreelekha T, Ramadas K, Pandey M, et al. Genetic polymorphism of CYP1A1, GSTM1 and GSTT1 genes in Indian oral cancer. *Oral Oncol* 2001;37:593-8.
- Chacko P, Joseph T, Mathew B, et al. Role of xenobiotic metabolizing gene polymorphisms in breast cancer susceptibility and treatment outcome. *Mutat Res* 2005;581:153-63.
- Balakrishnan V, Nair P, Radhakrishnan L, et al. Tropical pancreatitis - a distinct entity, or merely a type of chronic pancreatitis? *Indian J Gastroenterol* 2006;25:74-81.
- Balakrishnan V, R N, R L. Tropical Pancreatitis: What is Happening to it? In: Balakrishnan V, Sudhindran S, Kumar H, Unnikrishnan AG, eds. *Chronic Pancreatitis and Pancreatic Diabetes in India*. Bangalore: Indian Pancreatitis Study Group, 2006:23-54.
- Wilkinson J, 4th, Clapper M. Detoxication enzymes and chemoprevention. *Proc Soc Exp Biol Med* 1997; 216:192-200.
- Duell EJ, Holly EA, Bracci PM, et al. A Population-Based, Case-Control Study of Polymorphisms in Carcinogen-Metabolizing Genes, Smoking, and Pancreatic Adenocarcinoma Risk. *J Natl Cancer Inst* 2002;94:297-306.
- Schneider A, Togel S, Barmada M, et al. Genetic analysis of the glutathione s-transferase genes MGST1, GSTM3, GSTT1, and GSTM1 in patients with hereditary pancreatitis. *J Gastroenterol* 2004; 39:783-7.
- Hennie MJR, Robert JFL, Wilbert HMP, et al. Glutathione S-transferase mu null genotype affords protection against alcohol induced chronic pancreatitis. *American Journal of Medical Genetics Part A* 2003;120A:34-9.
- Whitcomb DC. Value of genetic testing in the management of pancreatitis. *Gut* 2004;53:1710-17.
- Goodsell DS. The Molecular Perspective: Polycyclic Aromatic Hydrocarbons. *Stem Cells* 2004;22:873-4.
- Conney AH. Enzyme Induction and Dietary Chemicals as Approaches to Cancer Chemoprevention: The Seventh DeWitt S. Goodman Lecture. *Cancer Res* 2003;63:7005-31.
- Li D, Jiao L, Li Y, et al. Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking, and risk of pancreatic cancer1. *Carcinogenesis* 2005;bgi71.

Extended Maxillectomy by Transmandibular Approach

S.S. Chatni, R. Sharan, S. Iyer, M.A. Kuriakose

ABSTRACT

OBJECTIVE

The objective of this study was to evaluate the effectiveness of mandibulotomy approach for maxillary sinus tumors with infra-temporal fossa extension.

STUDY DESIGN

This is a retrospective review of case records of patients who had undergone maxillectomy using trans-mandibular approach for tumors with infratemporal extension, for a period of 20 months from January 2004. For objective assessment of the morbidity profile of the procedure, all evaluable patients were recalled and evaluated using pre-defined parameters.

METHODS

From the institutional head and neck oncology database, all patients who have undergone maxillectomy and those requiring mandibulotomy approach for this procedure were identified. Details of the patient demographics, tumor details, radiological extent of the tumor, pathology report on resection margin, and patient status on follow up were obtained from the hospital records. Those patients who are disease free and have a minimum follow up of four months were evaluated for objective determination of the post-operative morbidity and effectiveness of the approach to obtain a surgical resection with uninvolved margin.

RESULTS

During the 36 months period from January 2004, 45 patients had undergone maxillectomy for malignant paranasal sinus tumors. Of these in ten patients the procedure was carried out using trans-mandibular approach and remaining using either Weber-Ferguson or mid-facial degloving approach. The indication for the trans-mandibular approach was maxillary sinus tumors with infra-temporal fossa involvement. Trans-mandibular approach was the sole procedure in six patients and additional Weber-Ferguson was required in two and craniotomy in two patients.

All patients had complete clearance with negative margins at the infratemporal fossa region. Varying degree of trismus was present in all patients. None of the patients had any complication at the mandibulotomy site. In two patients there were minor occlusal disturbances. The cosmetic result of the approach was satisfactory. Eight patients are free of disease, one patient has local recurrence and one patient died of recurrent disease.

CONCLUSIONS

Mandibulotomy is an effective approach for maxillary tumors with infra-temporal fossa extension. It can be combined with other approaches as required depending on the extent of tumor. The procedure has acceptable morbidity and the aesthetic and functional results are satisfactory.

Key words: Maxillectomy, Infratemporal fossa, Mandibulotomy, paranasal sinus cancer, skull base.

Extended Maxillectomy by Transmandibular approach

INTRODUCTION

Local recurrence is the most common pattern of treatment failure in maxillary sinus malignancies. This is particularly true in those maxillary sinus tumors with extension into infra-temporal fossa^{1,2}. Disease extension through the posterior wall into the pterygoid plates and infratemporal fossa are considered poor prognostic factors³. In these selected patients

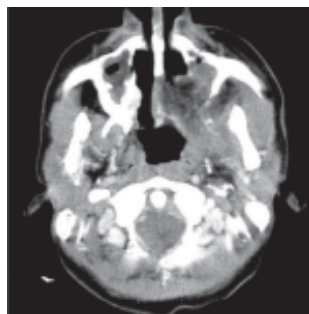


Fig. 1:CT scan showing disease extension through posterior wall of left maxilla and eroding the pterygoid plates

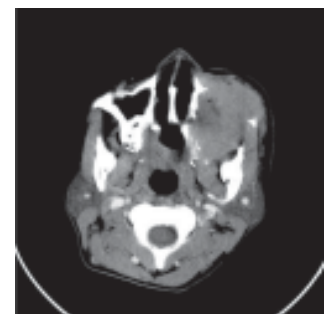


Fig.2 : CT scan showing disease in left maxilla, extending to the infratemporal fossa and anteriorly to the soft tissues of the cheek

(Fig.1, Fig.2), compartmental resection of the infratemporal fossa is required to obtain for an oncologically sound resection. This is difficult to obtain using the standard anterior approaches using Weber-Ferguson or facial degloving incisions^{4,5}. Mandibulotomy approach is a well-established technique to approach infratemporal fossa⁶. Herein we report effectiveness in performing extended maxillectomy with infra-temporal fossa clearance using mandibulotomy approach.

OBJECTIVE

The objective of this study was to describe the technique of mandibulotomy approach for excision of maxillary sinus tumor with extension to the infratemporal fossa as well as to evaluate the effectiveness and morbidity associated with the procedure.

MATERIALS AND METHODS

Head and neck oncology database of Amrita Institute of Medical Science was reviewed to identify all patients who have undergone maxillectomy during three-year period from January 2004 to January 2007. Reviewing of the patient records identified those patients who have undergone maxillectomy with mandibulotomy approach. Patient demographics, treatment details and follow up disease status were obtained from the patient records. The preoperative imaging studies were reviewed to assess the extent of tumour. The surgical resection margin was recorded from the histopathological report. The patients were recalled to assess morbidity profile using a pre-defined data sheet. The data point included- patient complaints, facial scar, complication at the mandibulotomy site, occlusal disturbances, mouth opening and disease status.

SURGICAL TECHNIQUE

A midline lip-splitting incision, which was extended to the neck, was utilized for the procedure (Fig.3). Intra-orally, the mucosal incision from the lower lip was extended to the alveolus and then to the ipsilateral premolar region as an inter-dental incision. After pre-adapting



Fig.3: Midline lip-split incision extending into the neck

bone plates, a para-median mandibulotomy was performed at the premolar and canine inter-dental area. Care is taken to identify and preserve the mental nerve. The inter-dental incision was then extended posteriorly on the medial side of mandible to the retro molar region in



Fig.4: Intra-oral incision extended to the upper gingivo-buccal sulcus anteriorly upto the proposed site of palatal cut. Medial Pterygoid plate divided at its insertion

a sub-periosteal plane. The incision was extended to the upper gingivo-buccal sulcus and then anteriorly till the intended site of palatal incision (Fig.4).



Fig.5: Vessel loop around the lingual nerve and the metal instrument pointing at the inferior alveolar nerve

The soft tissues are elevated off the medial side of mandible in a sub-periosteal plane; the medial pterygoid is divided at its insertion on the mandible (Fig.4). The inferior alveolar nerve and the lingual nerve are identified and preserved (Fig.5). Further the lateral pterygoid muscle is detached from the condyle of the mandible. The stylo-mandibular ligament and periosteal attachment at the posterior boarder of mandible was then released. The mandible can then be swung laterally to achieve good exposure of the infratemporal fossa and the middle cranial base. The internal maxillary artery can be visualized



Fig.6: Specimen with adequate posterior soft tissue margins

between the two heads of pterygoid muscles, which was ligated at this stage. The pterygoid plates are detached from the skull base to include in the specimen. The upper cheek flap is raised over the maxilla through the sub labial incision and further cuts are made to perform a maxillectomy. En bloc resection with adequate posterior soft tissue margins is thus achieved (Fig.6).

RESULTS

Transmandibular approach was utilized in ten out of 45 maxillectomies performed during the study period Table 1 summarizes the patient demographics and tumor details. Two patients were recurrent cases, having received prior treatment elsewhere. Table 2 describes the radiological extent, the surgical approaches used and the adequacy of resection. Of note, none of the patients had positive margin at the infratemporal fossa region.

All the patients in this series had reconstruction of the defects with free tissue transfer. Three patients received adjuvant radiotherapy, five patients received adjuvant concurrent chemoradiotherapy and two patients received no adjuvant therapy.



Fig.7: Postoperative picture showing reasonable cosmesis and trismus

Table 3 shows the complications related to the approach that were evaluated during the patients’ revisits. In spite of the jaw stretching exercises during the postoperative period, trismus was present in varying grades in all patients. The overall aesthetic result was very good (Fig.7).

One patient who had salvage surgery for recurrent spindle cell sarcoma of left maxillary sinus died after 20 months

Table 1: Patient demographics and tumor details

No	Age	Sex	Site	Histology
1	46	M	Maxilla- Left	Recurrent Spindle cell sarcoma
2	63	M	Maxilla- Right	Squamous cell carcinoma
3	32	F	Hard palate-Left	Mucoepidermoid carcinoma
4	37	F	Hard and soft Palate-Left	Adenoid cystic carcinoma
5	45	M	Maxilla- Right	Recurrent Inflammatory pseudotumor
6	45	F	Maxilla- Left	Squamous cell carcinoma
7	70	M	Maxilla- Left	Adenoid cystic carcinoma
8	50	M	Maxilla- Right	Mucoepidermoid carcinoma
9	32	M	Maxilla-Right	Squamous cell carcinoma
10	64	M	Hard and soft palate-Left	Squamous cell carcinoma

Table2: Extent of Pathology and Adequacy of the Approach Used

No	Tumor Extent			Surgical Approach	Resection status	Area of positive/ close margin
	Extra-cranial	Intra-cranial	Orbital			
1	Extension into ITF and Nasal Cavity	None	Intra-orbital; extra-conal	Weber-Ferguson with trans- conjunctival incision and Para-median mandibulotomy	R0	None
2	Extension into ITF and Nasal Cavity	None	None	Para-median mandibulotomy	R1	Posterior palatal mucosal margin
3	Hard palate, nasal cavity and ITF	None	None	Para-median mandibulotomy	R0	None
4	Extension to pterygo-maxillary region	None	None	Para-median mandibulotomy	R0	None
5	Extensions medially to nasal cavity and nasopharynx, posteriorly to ITF and superiorly to the middle cranial fossa	Extra-dural	Intra-orbital; extra-conal Periorbita preserved	Para-median mandibulotomy and fronto-temporal craniotomy	R0	None
6	Maxillary sinus with extensions to ITF and inferior orbital wall	None	Intra-orbital; extra-conal Periorbita preserved	Para-median mandibulotomy	R1	Orbital margin
7	Extensions to ITF and middle cranial base	Widening of foramen rotundum	None	Para-median mandibulotomy and temporal craniotomy	R1	V2 nerve cut margin
8	Extension to posterior wall of maxilla	None	None	Paramedian mandibulotomy	R0	None
9	Extension to ITF and ethmoids	None	Periorbita preserved	Paramedian mandibulotomy and lateral rhinotomy	R0	None
10	Minimal extension to ITF	None	None	Paramedian mandibulotomy	R0	None

Table3: Morbidity profile of mandibulotomy approach for maxillectomy

No	Scar	Occlusion	Osteotomy complications	Cranial nerve deficits	Mouth opening (cms)
1	Inconspicuous	Normal	Plate infection	V 3 sacrificed	2
2	Inconspicuous	Normal	None	Nil	2.5
3	Inconspicuous	Normal	None	Nil	2.5
4	Inconspicuous	Minimal deviation	None	V3 Anesthesia	1.5
5	Inconspicuous	Normal	None	Lingual nerve hypo aesthesia	1.5
6	Inconspicuous	Normal	None	Nil	2
7	Inconspicuous	Minimal deviation	None	Nil	2.5
8	Inconspicuous	Normal	None	Nil	2
9	Inconspicuous	Normal	None	V 3 sacrificed	2.5
10	Inconspicuous	Normal	None	None	3

following regional and distant metastasis. All other patients are alive till date with a median follow-up of 12 months, minimum follow-up being 2 months and maximum 29 months.

DISCUSSION

Extension of maxillary sinus carcinoma to pterygoid plates and infratemporal fossa is considered upstage the tumor to T4a⁷ and considered to have a poor prognosis⁸. There are also reports suggesting that infratemporal fossa involvement is not a poor prognostic factor in maxillary sinus cancer⁹.

When the paranasal sinus cancer involves pterygoid or the infratemporal fossa, for adequate surgical clearance compartmental resection of the infratemporal fossa contents along with the maxilla is required (Fig.1, Fig.2). With para-median mandibulotomy, the medial pterygoid muscle can be divided right from its insertions at the medial mandible and lateral pterygoid from the condyle and the temporal crest of infratemporal fossa. These muscles can be left attached to their origins at the pterygoid plates, which would be detached from the skull-base and removed with the maxilla. This posterior approach offers maximum visualization of the infratemporal fossa

region, which is poorly exposed through the conventional Weber-Ferguson, based anterior approach for maxillectomy. In addition, extension of the maxillary sulcus incision anteriorly as in is degloving approach allows performing the entire procedure through the lower lip-splint incision. When the tumor extends to the orbital floor or with intracranial extension, Weber-Ferguson (Fig.8) and bicoronal incisions (Fig.9) can be incorporated with the mandibulotomy approach, as the tumor dictates.

Although several techniques have been described to access infratemporal fossa¹⁰. The technique adopted by us is that described by R. M. Tiwari with some modifications in skin and mucosal incisions¹¹. Transmandibular approach to retro maxillary region was described by Barbosa in 1961¹². This approach was through the ascending ramus of the mandible and did not become popular. Transmandibular approach to the skull base was described by Biller et al in 1981¹³ and later adopted by Krespi et al in 1984¹⁴. They adopted a median mandibulotomy and summarized that this approach gives a good exposure to the lateral and midline compartments of the middle cranial base and a good vascular control in



Fig.8: Mandibulotomy combined with Weber Ferguson approach



Fig.9: Mandibulotomy combined with bicoronal incision for craniotomy

the neck. Para pharyngeal space, infratemporal fossa, clivus, nasopharynx and cervical spine can be exposed by this approach. Local recurrence due to inadequate posterior clearance in maxillary sinus cancers was well documented and various approaches were described to approach the infratemporal and retro maxillary regions. However they suffer from drawbacks of lateral mandibular osteotomy or limited exposure. Lawson et al for the first time in 1990 reported combined median mandibulotomy and Weber- Ferguson approach for total maxillectomy for the purpose of enbloc resection of pterygoid plates and infratemporal fossa muscles along with the maxillectomy specimen¹⁵. Again, no other reports of such approach are found in the literature after that. In 2001, R. M. Tiwari described the transmandibular approach to total maxillectomy. He advocated a paramedian mandibulotomy and the anteromedial dissection could be through the upper sub labial extension of the same approach¹¹. Other incisions can be added as necessary. As described by the same author, clearance of the retro maxillary area enbloc with the maxilla is the single most advantage of the technique. In addition to this, a Weber-Ferguson incision can be totally avoided in many instances. However, other approaches can be combined with this approach if necessary as shown in our series. Trismus is a common sequel but this is not related only to the approach because any surgery involving the infratemporal fossa results in trismus. Advantages of a Para-median

mandibulotomy over a median mandibulotomy are well established.

Conclusion: Mandibulotomy is the approach of choice for maxillary tumors with posterior extension. It gives good access for the clearance of the infratemporal fossa. It can be combined with other approaches as required depending on the extent of tumor. The cosmesis is good with reconstruction of the maxillectomy defects and the morbidity of the approach is minimal.

REFERENCES

1. Qureshi SS, Chaukar DA, Talole SD, et al. Squamous cell carcinoma of the maxillary sinus: a Tata Memorial Hospital experience. *Indian J Cancer* 2006 Jan-Mar;43(1):26-9.
2. Hicsonmez A, Andrieu MN, Karaca M, et al. Treatment outcome of nasal and paranasal sinus carcinoma. *Otolaryngol* 2005 Dec;34(6):379-83.
3. Dulguerov P, Jacobsen MS, Allal AS, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001 Dec 15;92(12):3012-29.
4. Choi EC, Choi YS, Kim CH, et al. Surgical outcome of radical maxillectomy in advanced maxillary sinus cancers. *Yonsei Med J* 2004 Aug 31;45(4):621-8.
5. Bilsky MH, Bentz B, Vitaz T, et al. Craniofacial resection for cranial base malignancies involving the infratemporal fossa. *Neurosurgery* 2005 Oct; 57(4 Suppl):339-47.
6. Jack LG, Lyon LG, Keith MW. Transmandibular approach. In: Paul J Donald. *Surgery of the Skull Base*. Philadelphia, PA:Lippincott-Raven; 1998:341-6.
7. AJCC staging manual 2002.
8. Carrillo JF, Guemes A, Ramirez-Ortega MC, et al. Prognostic factors in maxillary sinus and nasal cavity carcinoma. *Eur J Surg Oncol* 2005 Dec;31(10):1206-12.
9. Nazar G, Rodrigo JP, Llorente JL, et al. Prognostic Factors of Maxillary Sinus Malignancies. *Am J Rhinology* 2004 Jul;18(4):233-8.
10. Llorente JL, Nazar G, Cabanillas R, et al. Subtemporal-preauricular approach in the management of infratemporal and nasopharyngeal tumours. *J Otolaryngology* 2006 Jun 35(3):173-9.
11. Tiwari RM. Transmandibular Approach To Total Maxillectomy. *Indian Journal of Otolaryngology and Head and Neck Surgery* 2001;53:187-9.
12. Barbosa; 1961.
13. Biller RF, Shugar MA, Krespi YP. A new technique for wide field exposure of the base of the skull. *Arch Otolaryngol* 1981;107:698-702.
14. Krespi YP, Sisson GA. Transmandibular exposure of the skull base. *Am J Surg* Oct 1984;148(4):534-8.

Nasal Cure for a Myopathy- A Neuroendocrine Puzzle?

Siby G*, Syam UK*, Anandkumar A*, Hiran**, Aneesh G***

ACKNOWLEDGEMENT

The authors acknowledge departments of Head and neck surgery, Neurosurgery, Endocrinology and Pathology. We also thank Raju for his assistance in graphics of this manuscript.

THE SCENARIO

31 years old school teacher from a middle class family from Assam was admitted in head and neck surgery department, AIMS, Kochi, for evaluation of left nasal block with on and off epistaxis of 1yr duration. She was referred to neurology department for weakness of all limbs of 4 yr duration for which she was extensively investigated and treated in many major hospitals in India without much improvement.

“HERSTORY” DOWN THE LANE

This young lady was apparently up and about till 2002 during which, she used to take active participation in sports and dance. Since 2002 she started having recurrent generalized musculoskeletal pains with no history of arthritis or deformities or skin lesions. Subsequently she developed symmetrical proximal muscle weakness involving the lower limbs, however no distal weakness was noticed. This was followed by similar involvement of the upper limbs. Weakness gradually progressed and she became bedridden for the last 6 months despite treatment.

She did not have any diurnal variation of her symptoms; neither did she have any wasting, fasciculations, cramps or any other neuroaxial involvement. There was no history suggestive of any other systemic involvement till

last year. She also had no history suggestive of a toxic exposure or any similar illness in her family.

Neurological examination 4 yrs after the onset of illness revealed nasal twang of the voice and quadriparesis affecting predominantly proximal muscle groups of all extremities, neck & truncal muscles. It was associated with diffuse pain and bony tenderness. Reflexes were normally elicitable and plantars were bilaterally flexor. Sensory system examination revealed no abnor-

malities. Rest of the neurological examination was normal.

WHAT COULD BE THE NEUROLOGICAL LOCALIZATION?

Clinical possibility of a pure motor LMN syndrome was considered of which a muscle disorder appeared more likely. Other possibilities to be considered were NM Junction disorder, anterior horn cell disease,

Table 1:

Hemogram	Normal
Liver functions	Normal
Renal functions	Normal
Sodium	140 meq/l
Potassium	4.2meq/l
Bicarbonate	24 mmol/L
Magnesium	2.4 mg/dl (1.7-2.5)
Albumin	4 gm/dl
Serum Phosphorus	1.8 mg/dl (2.7-4.5)
Urine Phosphorous	5.5
Alkaline PO4	312 u/l (39-117)
Calcium	8.8 mg/dl (8.6-10)
25- OH Vit D	144.7 nmol/L (25-125)
PTH	77.75 pg/ml (16-62)
TSH	0.88 mIU/ml (0.2-4.2)
24 hrs urine Ca	171mg/24 hrs (100-300)
24 hrs urine phosphorus	434mg/24 hrs (400-1000)
24 hrs urine creatinine	972-mg/24 hrs
Tmp GFR	0.7 (2.5-4.5)

*Dept. of Neurology, **Dept. of Pathology, ***Dept. of Endocrinology, AIMS, Kochi.

proximal motor neuropathy and metabolic bone disease.

Going a step further, the temporal profile of the illness, absence of fluctuating weakness/ wasting/ fasciculations/ normal reflexes, narrow down the possibility to a muscle disease. Prior records from various hospitals showed that electrodiagnostic studies, serum CPK and muscle biopsy were all normal. She had also received steroids, but showed no response, thereby favouring the possibility of a metabolic myopathy rather than an inflammatory one.

FUEL FOR THOUGHT

She was investigated at various hospitals and found to have a raised alkaline phosphatase, normal calcium and low phosphorus, which was considered as secondary to hypovitaminosis D and hence she was put on Vit D and Calcium supplements without any improvement (she rather worsened).

WHY NO RESPONSE AFTER 4 YEARS OF APPROPRIATE TREATMENT WITH VITAMIN D AND CALCIUM???

SEEKING ANSWERS FROM LABORATORY AID'S:

Metabolic workup (Table 1) revealed hypophosphatemia with normal calcium & a high alkaline phosphatase. However, Serum Vit D3 and PTH levels were mildly elevated. Her tubular maximum for phosphate (TmP/GFR) corrected for GFR (index of renal threshold for phosphate, which is independent of plasma

Fig. 1: Multiple fractures of ribs and pelvis

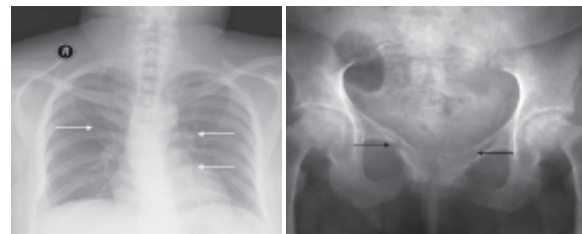


Fig. 1a

Fig. 1b

phosphate) was reduced. X-rays revealed multiple fractures at the site of maximum pain (Fig.1a & 1b). Whole body skeletal scintigraphy was performed which was suggestive of a metabolic bone disease rather than an infiltrative disorder.

Table 2: Biochemical findings in the major acquired conditions characterized by hypophosphataemia and musculoskeletal symptoms²

Condition	Plasma indices	Urinary indices
Nutritional osteomalacia	Calcium ↓ or low/normal 25 OH Vit D ↓ 1,25 Di OH Vit D ↓, normal or ↑ a PTH ↑ ALP ↑ b	Calcium ↓ Phosphate normal c
Oncogenic osteomalacia	Calcium normal 25 OH Vit D normal 1,25 Di OH Vit D ↓ or normal PTH normal or ↑ ALP ↑ b	Calcium normal Phosphate normal c
Primary hyperparathyroidism	Calcium ↑ 25 OH Vit D normal 1,25 Di OH Vit D normal or ↑ PTH ↑	Calcium normal d or ↑ Phosphate normal c
Humoral hypercalcaemia of malignancy (PTHrPe)	Calcium ↑ 25 OH Vit D normal 1,25 Di OH Vit D normal or ↓ PTH normal or ↓ ALP normal	Calcium ↑

a. Depends on any recent exposure to vitamin D. b. Occasionally within normal limits. c. But renal phosphate clearance always high. d. Owing to increased renal tubular reabsorption. e. Effects mediated by PTH-related peptide. Differences between the condition and primary hyperparathyroidism broadly reflect the effects of relative end organ resistance to PTHrP compared with PTH.

SUMMARIZING AT THIS JUNCTURE

Young female presenting with a chronic metabolic myopathy & multiple fractures which is non-responsive to appropriate dose of Vitamin D & calcium supplements, with persistent hypophosphatemia, phosphaturia (suggested by the reduced Tmp /GFR) and a mildly abnormal serum PTH & 25OH Vit D (despite significant hypophosphatemia)..

POSSIBILITIES???

Hypophosphatemic disorders¹ like –

- 1) Autosomal dominant hypophosphatemic rickets.
- 2) Acquired hypophosphataemic osteomalacia

(Table 2).

However, the age of onset, absence of significant family history and the characteristic biochemical profile further narrow down the diagnosis to oncogenic osteomalacia.

WHAT NEXT???

The patient was evaluated for an occult neoplasm. Usual sites were screened (Chest X-ray, USG abdomen, bone scan, genital examination) but yielded no additional information.

END OF THE ROAD???

PATIENTS ARE THE BEST TEACHERS (UNMASKING THE ETIOLOGY)

Now the patient presents with recurrent epistaxis and nasal block. On presentation she is bedridden for the last 6 months due to the pre-existing neurological problem mentioned above. She was evaluated by an ENT team outside and was diagnosed to have a nasopharyngeal mass lesion for which she was referred to head and neck team here for further management.

MRI of head and neck (Fig.2) showed a nasal mass with bone destruction of vomer, planum sphenoidale, and medial orbital wall with dural infiltration of planum sphenoidale.

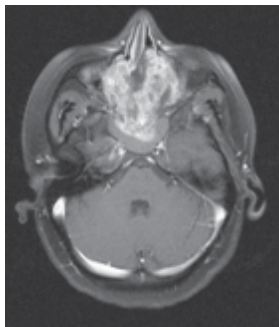


Fig.2: Nasal malignant tumour with bone destruction of vomer planum sphenoidal, medial orbital wall

WHAT COULD THE MASS BE???

FINAL COUNT DOWN

It is possible that the patient has 2 separate disease processes with the tumour being a separate entity. But, putting the traditional teaching of “Occam’s razor” into use, possibility of neuroendocrine tumours arising from the nasal region like esthesioblastoma or other soft tissue tumours were considered. However tumours like esthesioblastoma are not reported to be associated with osteomalacia, hence soft tissue tumours could be considered as the first possibility.

Hence the rare possibility of phosphaturic mesenchymal tumours, which are characterized by renal phosphate wasting (otherwise called oncogenic osteomalacia), was considered. Most tumours associated with oncogenic osteomalacia are benign, consisting of mesenchymal cells or mixed connective tissue, but occasional malignant ones are also reported³.

Bone lesions associated with oncogenic osteomalacia include hemangiopericytoma, osteosarcoma, chondroblastoma, chondromyxoid fibroma, giant cell tumour, malignant fibrous histiocytoma & giant cell tumour⁴. Soft tissue tumours are reported to be often vascular, with abundant spindle or giant cells.

Tumours are often small and not easily detectable on physical examination or on routine radiography. They appear to have a propensity for head and neck region, and detailed tomography or resonance imaging of the sinuses & jaw areas are advocated³. Successful localization of the causative tumours has been reported with octreotide scintigraphy or Tc⁹⁹-sestamibi scintigraphy⁵.

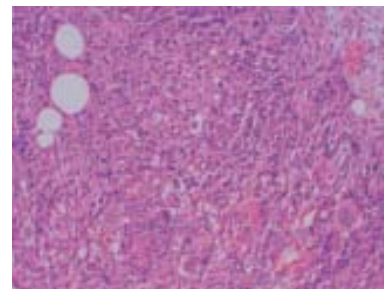


Fig.3a: H & E X 200 Admixed fat and giant cells

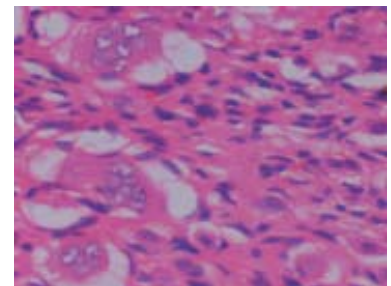


Fig.3b: H & E X 400 Giant cells and spindle cells

THE SURGEON'S PEN

Combined efforts from both Head & Neck with Neurosurgery teams were required for a successful resection of the tumour. Biopsy revealed (Fig.3) a benign mesenchymal tumour with giant cells

FINAL JUDGMENT

Phosphaturic mesenchymal tumour - mixed connective tissue variant.

THE PHYSICIAN'S COURT

She was discharged on oral phosphate solution with calcium & Vit D supplements. On follow up after 4 months, she had *full functional recovery* with normal serum Calcium & phosphorous levels. She is being maintained on oral phosphorus solution, calcium and Vitamin D3 supplements. If a tumour is not found or if an identified tumour is not resectable, it is recommended that 1 α -calcidiol, calcitriol or active Vitamin D metabolites and oral phosphates may be used³.

DISCUSSION

Osteomalacia is a well-recognized cause of metabolic myopathy particularly in women and the treatment is simple when the etiology is found with no difficulty. Oncogenic osteomalacia is a paraneoplastic manifestation of a specific mesenchymal tumor affecting soft tissues or bone.

The characteristic metabolic abnormalities of low serum phosphorus concentration, elevated alkaline phosphatase, and inappropriately high urine phosphate levels indicate hypophosphatemic osteomalacia due to renal phosphate wasting. Serum PTH levels are frequently normal but are reported to be variable also¹. Despite hypophosphatemia, which is a major physiological stimulus for 1,25-dihydroxy-vitamin D production, 1,25-dihydroxy-vitamin D levels is low or normal due to the suppression of 25OH vitamin D1 α hydroxylase by FGF-23⁶. These metabolic abnormalities were similar to those observed in our patient.

Muscle weakness in oncogenic osteomalacia is multifactorial. Hypophosphatemia, 1,25-dihydroxy-vitamin D deficiency, and disuse atrophy due to pain and fractures can all contribute to muscle weakness⁷.

Physiology minded physicians have been mind-boggled by the complexity involved in the pathogenesis of oncogenic osteomalacia.

FGF-23 (Fig-4) plays a central role in the proposed mechanism of renal phosphate wasting in these disorders. The tumor overexpresses FGF-23, which appears to be a phosphaturic peptide, "phosphatonin". It impairs the reabsorption of phosphate in the renal tubules and inhibits the 1-hydroxylation of 25-hydroxy-vitamin D in the kidney causing a decrease in the synthesis of 1,25-

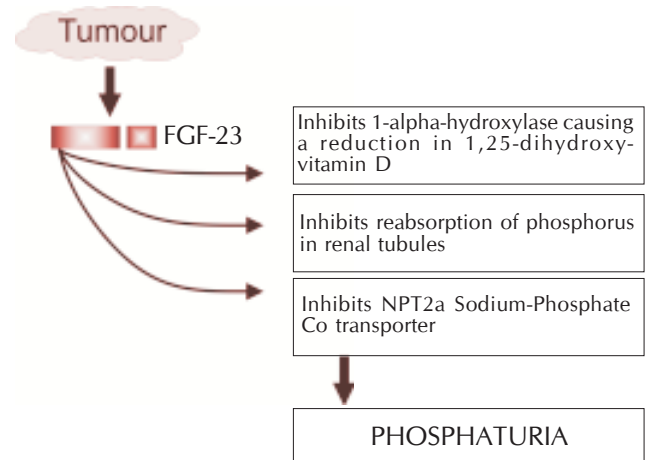


Fig.4: Role of FGF-23 in oncogenic osteomalacia⁸

dihydroxy vitamin D3, the deficiency of which is thought to cause renal phosphate wasting. FGF-23 also decreases NPT2a (sodium- phosphate renal co transporter) at proximal tubular cell thereby facilitating phosphaturia⁶.

In conclusion, treatment of oncogenic osteomalacia is a truly gratifying experience as there are not many medical conditions in which complete reversal of debilitating symptoms is possible with surgery (within few months). We propose that the basic investigation panel for a metabolic myopathy should include phosphorus levels, which can prevent a delay in diagnosis. Awareness of this condition and proper evaluation is a prerequisite for treatment of this condition without delay, as in our case the patient was doctor-shopping for almost 5 yrs. Neoplasm resection results in rapid correction of phosphate metabolism and gradual improvement of the metabolic bone disease and muscle weakness.

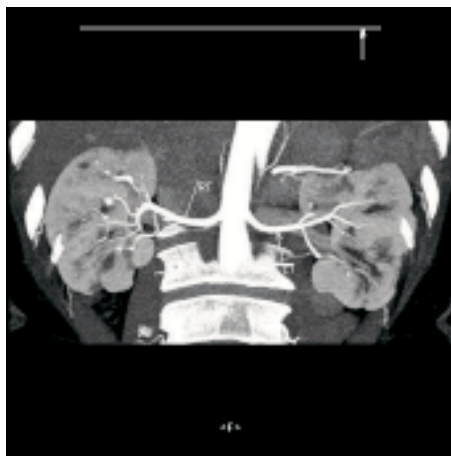
REFERENCES

1. Carpenter TO. Treatment of X-linked hypophosphatemic rickets. *Pediatr Clin North Am* 1997;44:443-66.
2. Clunie GPR, Fox PE, Stamp TCB. Four cases of acquired hypophosphatemic ('oncogenic') osteomalacia. *Problems of diagnosis, treatment and longterm management. Rheumatology* 2000;39:1415-21
3. Carpenter TO. Oncogenic osteomalacia-A complex dance of factors. *N Engl J Med* 2003;348;17:1705-8.
4. Park YK, Unni KK, Beabout JW, et al. Phosphaturic mesenchymal tumour. *J Korean Med Sci* 1994;9(4):289-98.
5. Nguyen BD, Wang EA. Indium-III Pentetreotide scintigraphy of mesenchymal tumour with oncogenic osteomalacia. *Clin Nucl Med* 1999;24;130-1.
6. Kronenberg HM. NPT2A-Key to phosphate homeostasis. *NEJM* 2002;347:1022-24.
7. Shafeeq SL, et al. Oncogenic osteomalacia: Muscular weakness and multiple fractures. *Neurology* 2006;67:364-5.
8. Jonsson KB, et al. FGF-23 in oncogenic osteomalacia & X-linked hypophosphatemia. *NEJM* 2003;348:1656-63.

Radiology Quiz

Chandramohan, R. Kannan, S. Moorthy

A 36 years old female with uncontrolled hypertension with retinopathy and generalized fatigue for 5 yrs referred for CT angiogram. CT angiogram of renal and abdomino pelvic images are shown. What is the most likely diagnosis?



Answer on Page 40

Rhinocerebral Mucormycosis in a Patient with Diabetic Nephropathy

A. Mathew , J.C. Varghese, P. Nair *, V.N. Unni

ABSTRACT

Diabetes Mellitus and immunosuppressed states predispose patients to fungal infections like mucormycosis: We report a case of rhino cerebral mucormycosis in a patient with diabetic nephropathy and moderate renal failure.

Key words : Rhinocerebral Mucormycosis, Diabetic Nephropathy

INTRODUCTION

Rhinocerebral mucormycosis is a life threatening infection that is associated with immunosuppressed states. The disease usually spreads rapidly; rarely, it may pursue an indolent course¹. In diabetic subjects, it is characteristically associated with diabetic ketoacidosis. This case report describes fulminant and progressive rhinocerebral mucormycosis in a subject with diabetic nephropathy (without ketoacidosis). In addition to the case report, a brief discussion with the relevant review of the literature is also presented.

CASE REPORT

A 45 years old manual labourer, a known diabetic since 15 years and hypertensive since six years, was admitted to our hospital with pain and progressive swelling of the left side of the face since one week. He was found to have very high blood sugar levels and moderate renal failure, and was referred to the Nephrologist for further treatment.

On admission he was febrile, conscious and oriented. BP was 160/100 mmHg. He had erythema and oedema over the left malar region of the face. Evaluation by ENT surgeon showed features of left maxillary sinusitis with sloughing of nasal mucosa. Optic fundi revealed non-proliferative diabetic retinopathy.

Investigations showed neutrophilic leucocytosis (21,000/cu.mm) with shift to the left and prominent toxic granules in neutrophils. Blood sugars were uncontrolled (FBS: 523mg/dl, PPBS: 698 mg/dl); he had proteinuria (1800 mg in 24 hours) and a moderate renal failure (S.Creatinine: 3.3mg/dl). Ultrasonogram showed normal sized kidneys with increased echogenicity. Roentgenogram of paranasal sinuses showed haziness of the left maxillary sinus. CT Scan of the paranasal sinuses showed soft tissue density occupying the left maxillary antrum and extending into the middle meatus with occlusion of the left osteomeatal complex (Fig.1). There was also extensive involvement of the anterior ethmoidal sinuses. He was started on antibiotics (Augmentin and Ofloxacin) as well as antihypertensives and blood sugars were controlled with Insulin



Fig. 1: CT Scan of the paranasal sinuses showing soft tissue density occupying the left maxillary antrum and extending into the middle meatus with occlusion of the left osteomeatal complex.

When he was initially seen by ENT surgeons he had only signs of left maxillary sinusitis. Within 36 hours, he developed an oroantral fistula on the left side along with sinus formation in the left lacrymal sac region (Fig.2). He was taken up for a Cald-Well Luc Surgery and left ethmoidectomy. Left maxillary antrum contained pus and sloughed mucosa and vascularity was impaired. Sloughed middle turbinate was excised and extensive debridement was done; specimens were sent for bacterial and fungal cultures and histopathology.

Histopathological examination of the sloughed nasal mucosa revealed

Dept. of Nephrology, * Dept. of Otorhinolaryngology, AIMS, Kochi.

the presence of broad non-septate fungal hyphae consistent with mucormycosis

(Figure 3a & b). He was started on Amphotericin B (1 mg/Kg/day as IV infusions).



Fig.2: Oroantral fistula on the left side along with sinus formation in the left lacrymal sac region.

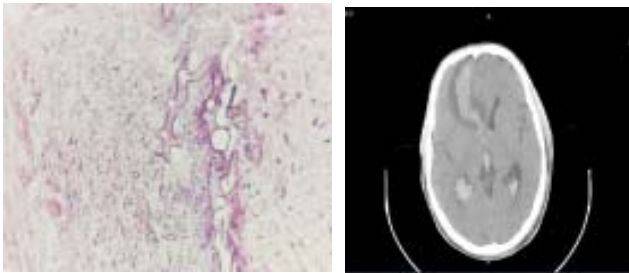


Fig.3b

Fig.3a

Fig.3a&b: Sloughed nasal mucosa showing the presence of broad non-septate fungal hyphae consistent with mucormycosis.

In spite of daily irrigation and suction, the general condition of the patient did not improve. On 8th day after admission his sensorium deteriorated rapidly. Though he did not show any focal neurological signs, fundus examination showed bilateral papilloedema. A non-contrast CT Scan of the brain showed a right frontal lobe hematoma causing mild oedema and mass effect with extension of the bleed into lateral, 3rd and 4th ventricles (Fig.4). A digital subtraction angiogram was done but no definite source of bleed could be demonstrated. Neurology and Neurosurgery opinion was sought and conservative management was advised.

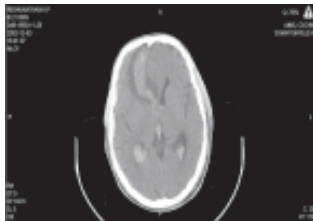


Fig.4: Non contrast CT Scan of the brain showing a right frontal lobe hematoma causing mild oedema and mass effect with extension of the bleed into lateral, 3rd and 4th ventricles.

In spite of antifungal therapy, antibiotics and other supportive measures, patient continued to have high-grade fever and worsening of the sensorium. On 17th day after admission, he developed further deterioration in sensorium and expired on the 19th day.

DISCUSSION

The Zygomycetes are a class of fungi that can cause a variety of infections in humans. These fungi are ubiquitous in nature and can be found on decaying vegetations and in the soil. The genera most commonly seen in human infections are *Rhizopus*, *Absidia*, *Mucor* and *Cunninghamella*. The hyphae of Zygomycetes fungi are distinct in nature, a feature that allows presumptive identification from clinical specimens. The hyphae are broad, irregularly branched and have very rare septations.

Mucormycosis is characterised by infarction and necrosis of host tissues that results from invasion of the vasculature by the hyphae. The infection usually spreads very fast, but there are rare descriptions of infections with an indolent course¹. Almost all patients with invasive mucormycosis have some underlying disease that predisposes to the infection and influences the clinical presentation. The most common underlying conditions are metabolic acidosis, diabetes mellitus, hematological malignancies, solid organ transplantation, acquired immunodeficiency syndrome (AIDS), trauma, burns, treatment with corticosteroids or Desferoxamine².

The most common clinical presentation of mucormycosis is rhinocerebral infection¹. The infection is thought to start with inhalation of spores into the paranasal sinuses (PNS) of a susceptible host. Hyperglycemia, usually with an associated metabolic acidosis, is the most common underlying condition found in patients with rhinocerebral mucormycosis². A review of 179 cases of rhinocerebral mucormycosis found that 126 (70%) of the patients had diabetes mellitus and most had ketoacidosis at the time of presentation². There are very rare reports of rhinocerebral mucormycosis in the absence of any apparent risk factors³.

The infection usually presents as an acute sinusitis with fever, purulent nasal discharge and pain over the sinuses; all the sinuses may get involved. Spread of infection from sinuses to contiguous structures such as the palate, orbit and brain commonly occurs very quickly. The indicators of spread beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of the turbinates, perinasal swelling, erythema and cyanosis of the facial skin overlying the involved sinuses.

Periorbital oedema, proptosis and blindness occur with involvement of the orbit. Spread of the infection from

the ethmoid sinuses to the frontal lobe results in obtundation. Spread from the sphenoid sinuses to the adjacent cavernous sinus can result in thrombosis of the sinus itself and involvement of the carotid artery.

Isolated involvement of the Central Nervous System.

Though central nervous system (CNS) infection typically arises from an adjacent PNS infection, there have been more than 30 cases of isolated CNS mucormycosis described in literature⁴. Over two-thirds of patients with isolated CNS mucormycosis have been intravenous drug abusers, who presumably have injected material contaminated with zygomycetes spores directly into the blood stream. Most of the patients presented with lethargy and focal neurological deficits. The vast majority of patients had involvement of the basal ganglia although isolated involvement of the frontal lobe has also been described⁴.

RENAL MUCORMYCOSIS

Isolated involvement of the kidneys with mucormycosis has been reported and is presumed to occur via seeding of the kidneys during an episode of fungaemia⁵. Many of the patients with isolated renal involvement also are infected with human immunodeficiency virus. Patients with this form of mucormycosis usually present with flank pain and fever and involvement can be unilateral or bilateral⁶.

MANAGEMENT

The diagnosis of mucormycosis is made by identification of the organism in tissues with an inflammatory reaction and often necrosis of the tissue involved. A clinician must think of this entity and pursue invasive testing in order to establish a diagnosis as early as possible. Rhino cerebral infection should be suspected in any high-risk patient that presents with sinusitis. Though rhino cerebral mucormycosis has classically been associated with diabetic ketoacidosis, it can also occur in the absence of ketosis, as in this case. Endoscopic evaluation of the sinuses should be performed to look for tissue necrosis and to obtain specimens. The specimens should be inspected for hyphae using Calcofluor white and methanamine silver stains. However the absence of hyphae should not dissuade clinicians from considering a diagnosis of mucormycosis when the clinical picture is highly suggestive.

Further evaluation includes imaging of the head with either CT or MRI to gauge sinus involvement and to evaluate the contiguous structures of the brain. For isolated renal involvement, percutaneous biopsy or nephrectomy can establish a diagnosis⁶.

The mainstay of treatment of mucormycosis is early surgical intervention, if this can be performed. Aggres-

sive (often radical and disfiguring) surgical debridement should be undertaken as soon as the diagnosis of the rhino cerebral mucormycosis is strongly suspected. Adjuvantive therapy with Amphotericin B (1mg/ Kg/day as IV infusions) is advised. Liposomal formulations have been used in some patients and this is indicated in patients intolerant to conventional Amphotericin B⁷.

Despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is not favourable. Absence of pulmonary involvement, surgical debridement, and a cumulative dose of Amphotericin-B more than 2000mg were associated with a better outcome². In rhino cerebral mucormycosis, patients usually present with advanced disease and the prognosis is poor. The most significant factors associated with death were delayed diagnosis, the presence of hemiplegia or hemiparesis, bilateral sinus involvement, leucopenia, renal disease and treatment with Desferoxamine². Overall mortality from rhino cerebral mucormycosis ranges from 25 to 50 percent, with the best prognosis in patients with infection confined to the sinuses.

As Physicians encounter and treat a large number of diabetic patients with renal failure, as well as follow up renal transplant recipients (on immunosuppression), it would be essential to be fully aware of this fungal infection; a very early diagnosis and prompt treatment are extremely crucial to save the lives of these patients.

REFERENCES

1. Harill WC, Stewart MG, Lee AG, et al. Chronic Rhino cerebral Mucormycosis. *Laryngoscope* 1996;106:1292-97.
2. McNulty JS. Rhino cerebral Mucormycosis: Predisposing factors. *Laryngoscope* 1982;92:1140-3.
3. Radner AB, Witt MD, Edward JE. Acute Invasive rhino cerebral mucormycosis in an otherwise healthy patient. Case report and review. *Clin Infect Dis* 1995;20:163-7.
4. Hopkins RJ, Rothman M, Fiore A, et al. Cerebral mucormycosis associated with intravenous drug use. Three case reports and review. *Clin. Infect. Dis.* 1994;19:1133-7.
5. Langston C, Roberts DA, Porter GA, et al. Renal Phycomycosis. *J Urol* 1973;109:941-4.
6. Levy E, Bia Mj. Isolated Renal Mucormycosis. Case report and review. *J. Am. Soc. Nephrol* 1995;5:2014-7.
7. Herbrecht R, Letscher – Bru V, Bowden RA. Treatment of 21 cases of invasive mucormycosis with Amphotericin B colloidal dispersion. *Eur. J. Clin. Microbiol. Infect. Dis.* 2001;20:460-4.

Multiple Endocrine Neoplasia 2B

N.M. Detroja, B. Nisha, A.G. Unnikrishnan

ABSTRACT

Multiple endocrine neoplasia type 2 B (MEN2B) is a very rare condition characterized by bilateral pheochromocytomas, medullary thyroid carcinoma (MTC) and mucosal neuromas in association with a marfanoid habitus. A high degree of suspicion is essential in evaluating subjects who present with isolated components of the syndrome, since both pheochromocytomas and MTC are potentially life-threatening conditions. We report a case of MEN2B who presented with mucosal neuromas years ago to a local doctor, followed several years later by the eventual development of the full-blown syndrome.

ACKNOWLEDGMENTS

We are thankful to Dr. Gopalkrishnan Nair and Dr. Sheela Nampoothiri for their contribution in the case management.

CASE

A 40-year-old gentleman came with history of swelling in front of neck first noticed 6 months back. The swelling had been rapidly increasing in size for past 3 months. Clinically, he was euthyroid and there were no pain or pressure symptoms. He was evaluated outside; FNAC of the thyroid nodule was suggestive of medullary thyroid carcinoma (MTC) and was referred to our department for further management. His mother had noticed multiple small swelling over tongue and lips since childhood; however, this was not evaluated and he had earlier undergone plastic surgery of lips for the same in 1984 (Fig.1 and 2).

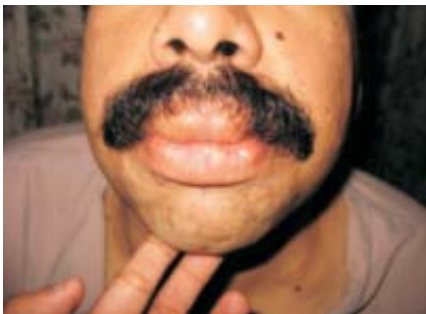


Fig.1: Showing 'bumpy lip' due to mucosal neuromas

Dept. of Endocrinology & Diabetes, AIMS, Kochi.

He was overweight and had a marfanoid habitus. His blood pressure was persistently normal. He had acanthosis nigricans and mucosal neuromas over the lips and tongue. A solitary thyroid nodule measuring around 3 x 3 cm in size was present over the right lobe of the thyroid. This nodule was hard, moving and non-tender. He also had bilateral cervical lymphadenopathy.



Fig.2: Mucosal neuromas over tongue

In view of the FNAC of MTC and mucosal neuroma he was thought to have Multiple Endocrine Neoplasia 2B (MEN2B) and was investigated further. His thyroid functions were normal and S. Calcitonin and Carcino Embryonic Antigen (CEA) were elevated (Table 1).

Table 1: Laboratory investigations of the patient

Free T4	1.37 ng/dL (normal 0.93 – 1.71)
TSH	1.32 mU/L (normal 0.27 – 4.2)
Calcitonin	1349 pg/mL (normal 0 – 18.2 pg/ml)
CEA	190.5 ng/mL (normal < 3 ng/ml)
24 hour urinary VMA	1.8 mg/24 hour (normal < 8)
24 hour urinary metanephrine	0.4 mg/24 hour (normal < 1)
Calcium	8.7 mg/dL (normal 8.6 – 10.2)
Parathormone	68.8 pg/mL (normal 16 – 62)

CT scan neck showed multiple nodules involving both lobes of thyroid with evidence of multiple enhancing lymphadenopathy in the submandibular level 2, 3, 4 right side and level 1 and 5 on both sides. The 24-hour urinary metanephrine and VMA were surprisingly normal. CT abdomen showed a 6.2 x 5.8 cm sized heterogeneously enhancing lesion with central necrosis on the left adrenal gland. Right adrenal gland also showed evidence of 1.2 x 1.3 cm enhancing nodule (Fig.3).

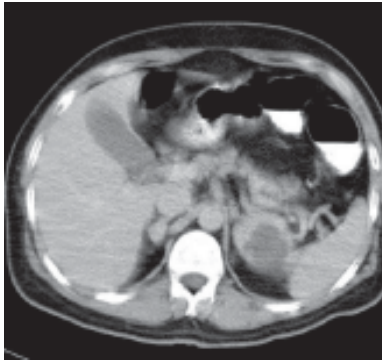


Fig.3: CT chest showing bilateral adrenal mass lesion

In spite of normal VMA and metanephrine patient underwent laparoscopic bilateral adrenalectomy in view of presence of bilateral adrenal mass and strong possibility of the pheochromocytoma in this clinical setting. Before surgery he was adequately prepared with alpha blockade and given peri and postoperative steroid coverage and later on, after adrenalectomy, he was stabilised on oral hydrocortisone and fludrocortisone. His diagnosis was confirmed with histopathology showing bilateral pheochromocytoma. After that he underwent total thyroidectomy with bilateral modified radical neck dissection. Histopathology confirmed the diagnosis of MTC with metastasis to bilateral cervical lymph nodes. Post operatively he was started on L-thyroxine replacement and then fractionated radiotherapy was given to tumor bed and nodal areas.

MUTATION ANALYSIS

His blood was sent for MEN2B mutation analysis which was done by PCR DNA sequencing which revealed a heterozygous M918T mutation in exon 16 of RET proto-oncogene of chromosome 10. His diagnosis of MEN 2B was confirmed.

CARRIER ASCERTAINMENT

His 3-year-old son's blood was also sent to the same laboratory and it also yielded the same M918T mutation. The son had few mucosal neuromas in the tongue. His BP was normal and basal calcitonin was 14 pg/mL.

He underwent total thyroidectomy with central compartment dissection.

Histopathological examination showed C cell hyperplasia. His urinary metanephrines and CT abdomen are normal now.

DISCUSSION

Multiple endocrine neoplasia syndromes are classified into two main categories: MEN type 1 and MEN type 2

MEN 2 includes two forms:

MEN 2A (Werner's syndrome)

-Medullary thyroid cancer (100%)

-Pheochromocytoma (50%) and

-Parathyroid tumors (10-20%)

MEN2A variants

-MEN2A with cutaneous lichen amyloidosis

-Familial Medullary thyroid cancer

-MEN2A with Hirschsprung's disease

MEN2B

-Medullary thyroid cancer (100%)

-Pheochromocytoma (50%)

-Ganglioneuroma and mucosal neuromas (> 98%)-

-Marfanoid habitus (> 95%)

MEN2 related syndromes are uncommon with probably fewer than 1500 kindreds worldwide¹. Fewer cases of MEN2 have been reported in Asia, except for Japan, where many families exist². They are autosomal dominant conditions due to activating mutations of extracellular cysteine domain or intracellular tyrosine kinase domain of RET protooncogene with the result that the intracellular tyrosine kinase is activated constitutively in the absence of its natural ligand 'Glial derived neurotrophic factor'. MTC occurs in all the patients of MEN2B. In general MTC develops earlier and it is more aggressive in MEN2B compare to MEN2A. Children have been described with metastatic MTC shortly after birth^{3,4}. Death related to complications of metastatic MTC may occur before onset of the third decade^{5,6}. Pheochromocytomas in MEN2B occur in more than 50% of affected individuals and also may develop at an early age. Mucosal neuromas located on the tongue tip, within the lips, and on the eyelids makes for a characteristic facies identifiable even in the childhood⁷. But because of the rarity of the condition and unawareness amongst the doctors it is often missed as in the present case.

The primary goal of screening for MEN2 is to identify and treat the several manifestations of MEN2 before they become life threatening. A secondary goal is to provide genetic counseling to family members about the potential for transmission to the next generation. The two

life-threatening manifestations of MEN2 are metastasis from MTC and sudden death caused by pheochromocytoma. Carriers of RET mutation are classified into three categories of risk. The highest risks are those with MEN2B and a codon 918, 883 or 922 mutation. They should undergo total thyroidectomy and central lymph node dissection ideally in the first month of life and latest before 6 months of age as metastases have been reported as early as first year of life. The high-risk cases are those with mutations in 609, 611, 618, 620 and 634 and require total thyroidectomy before 5 years of age. The intermediate risk is for those with 768, 790, 791 or 804 mutation and they require thyroidectomy when stimulated calcitonin values are high. Some do surgery at the age of 10 years. Tests for pheochromocytoma has to be done yearly⁸.

In summary, early carrier ascertainment and treatment by total thyroidectomy at an early age appear to identify and treat patients before there is identifiable lymph node metastasis. Thus it is possible that death from hereditary MTC will be largely eliminated by this early intervention, making it the first example of successful use of genetic ascertainment to eliminate death from malignancy. However, it will be many years before the impact of this earlier intervention on cure of MTC will be demonstrated.

REFERENCES

1. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogen mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA* 1996;276:1575-79.
2. Yamamoto M, Takai S, Miki T, et al. Close linkage of MEN2A with RBP3 locus in Japanese Kindreds. *Hum Genet* 1989;82:287-8.
3. Moyes CD, Alexander FW. Mucosal neuroma syndrome presenting in a neonate. *Dev Med Child Neurol* 1977;19:518-34.
4. Samaan NA, Draznin MB, Halpin RE, et al. Multiple endocrine syndrome 2b in early childhood. *Cancer* 1991;68:1832-34.
5. Sizemore GW, Carney JA, Gharib H, et al. Multiple endocrine neoplasia type2B: Eighteen-year follow-up of a four-generation family. *Henry Ford Hosp J* 1991;40:1832-34.
6. Vasen HFA, Van der Feltz M, Raue F, et al. The natural course of multiple endocrine type 2b: a study of 18 cases. *Arch Intern Med* 1992;152:1250-2.
7. Rashid M, Kairi MR, Dexter RN, et al. Mucosal neuroma, pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine (Baltimore)* 1975; 54:89-112.
8. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658-71.

Radiology Quiz

Chandramohan, R. Kannan, S. Moorthy

DIAGNOSIS:
Polyarteritis Nodosa.

DISCUSSION:

Polyarteritis Nodosa is a systemic fibrinoid necrotizing vasculitis of medium sized and small muscular arteries (and sometimes small veins) that can involve any organ and in varying degrees.

PAN occurs twice as frequently in men as in women, and it is found in all age groups but most commonly in the 5th–7th decades.

The kidneys may be involved in 70%–80% of cases; the gastrointestinal tract, peripheral nerves, and skin in 50%; skeletal muscles and mesentery in 30%; and the central nervous system in 10%.

Many of the clinical symptoms are related to organ ischemia secondary to arterial branch occlusions. Aneurysm rupture is a less common cause of pain. Arthralgias are noted in 50% of patients, as are peripheral neuropathies. Renal involvement including proteinuria and hypertension are found in 75%. Branch vessel occlusions can lead to multiple renal infarcts.

A definitive diagnosis may be made in certain clinical settings by performing tissue biopsy from a symptomatic organ site.

Angiography is considered the gold standard for diagnosis. The main angiographic findings in polyarteritis nodosa are small aneurysms, vascular ectasia, and occlusive vascular disease manifesting as luminal irregularity, stenosis, or occlusion of small and medium-sized arteries of the viscera. These abnormalities are detected in 40–90% of patients who have just developed clinical symptoms.

The most well known angiographic feature is the presence of so-called microaneurysms in medium or small arteries.

CECT can demonstrate aneurysms of the hepatic, pancreatic, and renal arteries and lesions inside these organs caused by either aneurysm rupture or thrombosis. MDCT can be used as a noninvasive imaging technique for diagnosing small aneurysms in patients with suspected polyarteritis nodosa and for following up these patients after immunosuppressive treatment.

In this particular case multiple microaneurysms were detected in both renal arteries. Multiple small infarcts were noted in both the kidneys producing a moth eaten appearance. Aneurysms were also noted in the splenic artery and internal iliac artery branches and lab investigations revealed Positive ANA, elevated as DNA antibody and elevated ESR were detected.

Cases, Evidence and Verdicts - The Glitazone Controversy

T. Roy, T. Rony, A.N. Babu

There have been a number of reports and significant controversy over the cardiovascular safety of the thiazolidinediones, and in particular, rosiglitazone. The fifth installment of this series reviews three recent articles related to PPAR γ agonists – **Thiazolidinediones or Glitazones**. Abstracts of the studies as they appeared in print are presented, followed by an analytical commentary.

Erland Erdmann MD, FESC, FACC, John A. Dormandy FRCS, DSc, Bernard Charbonnel MD, Massimo Massi-Benedetti MD, Ian K. Moules BSc (Hons), Allan M. Skene PhD and PROactive Investigators

The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction

Results From the PROactive (PROactive 05) Study

Journal of the American College of Cardiology Vol 49, No. 17, 1 May 2007

INTRODUCTION

People with type 2 diabetes have an increased incidence of MI compared with the general population. Those with diabetes and MI have a worse prognosis than nondiabetic patients with cardiovascular disease.

OBJECTIVES

This analysis from the PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) study

assesses the effects of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes and a previous myocardial infarction.

METHODS

The PROactive study was a prospective, multicenter, double-blind, placebo-controlled trial of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to either pioglitazone or placebo in addition to their other glucose-lowering and cardiovascular medication. Treatment of diabetes, dyslipidemia, and hypertension was encouraged according to the International Diabetes Federation guidelines. Patients were followed for a mean of 2.85 years. The primary end point was the time to first occurrence of macrovascular events or death. Of the total cohort, the subgroup of patients who had a previous MI (n = 2,445 [46.7%]; n = 1,230 in the pioglitazone group and n = 1,215 in the placebo group) was evaluated using prespecified and post-hoc analyses.

RESULTS

Pioglitazone had a statistically significant beneficial effect on the prespecified end point of fatal and nonfatal MI (28% risk reduction [RR]; p = 0.045) and acute coronary syndrome (ACS) (37% RR; p = 0.035). There was a 19% RR in the cardiac composite end point of nonfatal MI (excluding silent MI), coronary revascularization, ACS, and cardiac death (p = 0.033). The difference in the primary end point defined in the

main PROactive study did not reach significance in the MI population (12% RR; p = 0.135). The rates of heart failure requiring hospitalization were 7.5% (92 of 1,230) with pioglitazone and 5.2% (63 of 1,215) with placebo. Fatal heart failure rates were similar (1.4% [17 of the 92] with pioglitazone versus 0.9% [11 of the 63] with placebo).

CONCLUSIONS

In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS.

The PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) was a prospective, randomized, multicenter, double-blind, placebo-controlled trial involving 5,238 patients with type 2 diabetes and macrovascular disease. A subanalysis of those with a previous history of myocardial infarction (MI) (n = 2,445) showed that pioglitazone had a statistically significant benefit on recurrent MI (28% risk reduction) and acute coronary syndrome (37% risk reduction). We conclude that pioglitazone was effective in the secondary prevention of atherosclerotic disease in high-risk patients with type 2 diabetes and a previous MI.

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes.

NEJM: Vol 356:2457-2471 June 14, 2007

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; $P=0.03$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; $P=0.06$).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. The study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. The Lancet, Volume 368, Issue 9549, 18 November 2006-24 November 2006, Page 1770

BACKGROUND

Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability

to prevent type 2 diabetes in individuals at high risk of developing the condition.

METHODS

5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; $n=2365$) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat.

RESULTS

At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11.6%) individuals given rosiglitazone and 686 (26.0%) given placebo developed the composite primary outcome (hazard ratio 0.40, 95% CI 0.35–0.46; $p<0.0001$); 1330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) in the placebo group became normoglycaemic (1.71, 1.57–1.87; $p<0.0001$). Cardiovascular event rates were much the same in both groups, although 14 (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure ($p=0.01$).

CONCLUSION

Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.

COMMENTARY

Before the introduction of glitazones, conventional management of type 2 diabetes involved lifestyle modifications, sulfonylureas, and metformin. Thiazolidinediones or glitazones were first introduced for the treatment of type 2 diabetes in 1996. They uniquely target insulin resistance—a core physiologic defect in those with type 2 diabetes and thus significantly improve glucose control. They improve insulin action in muscle, adipose, and hepatic tissue by acting as agonists of peroxisome proliferator-activated receptor - γ (PPAR- γ) nuclear receptors. Activation of PPAR- results in a myriad of both metabolic and vascular effects by upregulating and downregulating expression of numerous genes, including genes known to regulate lipid and glucose metabolism, vascular function, thrombotic function, and the inflammatory response¹.

Results from PROactive 05 Study concluded that pioglitazone significantly reduced the occurrence of fatal

and nonfatal MI and acute coronary syndromes in high-risk patients with type 2 diabetes and previous MI. Insulin resistance contributes to the development of hyperglycemia as well as to a cluster of characteristic CVD risk factors, including an atherogenic lipid profile; hypertension; and a prothrombotic, proinflammatory vascular environment². Improving insulin sensitivity can lower blood glucose, improve plasma lipids, lower blood pressure, and improve many of the characteristic vascular abnormalities common in those with type 2 diabetes³. Pioglitazone has a favorable effect on lipid levels (increases HDL, lowers triglycerides and beneficially changing the composition of LDL particles), blood pressure and mediators of inflammation and endothelial dysfunction⁴. It also reduces intima-media thickness of the carotid artery⁵.

The second article we have presented is a meta-analysis which heralded the onset of the current controversy regarding cardiovascular safety when it concluded that rosiglitazone was associated with a significant increase in risk of myocardial infarction and risk of death from cardiovascular causes that had borderline significance. The mechanisms for the apparent increase postulated by the authors were as follows:

A mean increase in LDL cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo⁶.

(a) They are known to precipitate congestive heart failure in susceptible patients⁷; which can increase the myocardial oxygen demand and thus could provoke ischaemic events.

(b) Modest reduction in hemoglobin

However the conclusions were based on limited access to trial results from publicly available sources, not on patient level source data. Results were based on a relatively small number of events, resulting in odds ratio that could be affected by small changes in the classification of events. The confidence interval for the odds ratio for MI and death are wide, resulting in uncertainty about the magnitude of the observed hazard.

Adding to the uncertainty, the recently published RECORD⁸ study (which was reported after the metanalysis) concluded that there was no evidence of increased mortality, either from any cause or from cardiovascular causes. There was however a significant increase in risk of heart failure. This was a large, randomized, long-term study involving patients with type 2 diabetes. This was designed to assess the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea, as compared with the combination of metformin and sulfonylurea. This interim report was generated in response to the meta-analysis described above, and is based on 4447 participants with a mean follow up of 3.75 years. However this study was significantly un-

derpowered because of the withdrawal of patients from their assigned treatment and losses to follow-up. Accompanying editorials in the NEJM expressed concern that if anything, the RECORD data suggested the possibility of harm and certainly did not dispel such concerns^{9,10,11}.

The DREAM study, reported in the third article we have considered, concluded that rosiglitazone at 8 mg daily for 3 years together with lifestyle modifications substantially reduces the risk of diabetes by 60% in individuals at high risk of diabetes. It also increased the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both. The explanations postulated by the authors were as follows. Rosiglitazone increases the effectiveness of endogenous insulin. It could slow the fall in beta cell function with time by reducing the physiological demand for insulin secretion or by direct beta cell cytoprotective effect¹². There was a seven-fold increase in heart failure incidence in the rosiglitazone group, though in absolute terms this was still relatively modest with an incidence of 0.5%. There was no other statistically significant difference in cardiovascular complications though for major outcomes like myocardial infarction, there was a trend towards increased incidence with rosiglitazone.

Whether the observed cardiovascular risks of rosiglitazone represent a "class effect" of thiazolidinediones is to be considered. PROACTIVE study (article A) showed a significant effect favoring pioglitazone. Pioglitazone has a more favourable effect on lipids than rosiglitazone. Relative to rosiglitazone, pioglitazone improves triglycerides, HDL-C, non-HDL-C, and LDL particle concentration and size. However muraglitazar, dual PPAR γ and PPAR α agonist was disapproved by FDA due to increase cardiovascular events¹³. The weight of evidence to date suggests that the risks are *not* uniform between the thiazolidinediones, with pioglitazone apparently showing benefits, and rosiglitazone harm.

The Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) convened on 30 July 2007 to discuss the myocardial ischemic risk associated with rosiglitazone treatment¹⁴. They concluded that the use of rosiglitazone was associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylureas. Ultimately, the committee voted to recommend not that rosiglitazone be removed from the market but rather that label warnings and extensive educational efforts be instituted immediately. The committee also requested further studies, but disconcertingly, none of the several proposed analyses of the ongoing clinical trials is likely to define an absolute risk for myocardial ischemic events in patients with diabetes who are taking this drug.

What would be reasonable conclusions to draw from these varying results?

1. Thiazolidinediones are approved monotherapy agents in treatment of type 2 diabetes mellitus. They are also indicated for use in combination with sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control. However they should be used cautiously, if at all, in those with cardiovascular disease.
2. They may be used in those with IFG/IGT with high risk of diabetes.
3. Pioglitazone would clearly seem to be preferable to rosiglitazone in view of its favorable lipid lowering profile and less cardiovascular events and can be considered the agent of choice if a thiazolidinedione is required.
4. The treating clinician should carefully consider the need for any thiazolidinedione before prescribing one and should refrain from using rosiglitazone in the absence of exceptionally compelling circumstances.

REFERENCES

1. Miyazaki Y, Mahankali A, Matsuda M, et al. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 2001;24:710-9.
2. Kendall DM, Sobel BE, Coulston AM, et al. The insulin resistance syndrome and coronary artery disease. *Coron Artery Dis* 2003;14:335-48.
3. Hamdy O, Ledbury S, Mullooly C, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. *Diabetes Care* 2003;26:2119-25.
4. Kendall DM, Buse JB, Boyle PJ, et al. Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycemic control in patients with type 2 diabetes. *Curr Med Res Opin* 2004;20:215-23.
5. Langenfeld MR, Forst T, Hohberg C, et al. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus. Results from a controlled randomized study. *Circulation* 2005;111:2525-31.
6. Avandia (rosiglitazone maleate) tablets: prescribing information. Research Triangle Park, NC: GlaxoSmithKline, 2007 (package insert).
7. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association: October 7, 2003. *Circulation* 2003;108:2941-8.
8. Philip DH, D Phil, Stuart J, et al. Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis. *NEJM* 2007;357:28-38.
9. Bruce MP, Curt DF. The Record on rosiglitazone and the risk of myocardial infarction. *NEJM* 2007;357:67-9.
10. David MN. Rosiglitazone and cardiotoxicity – Weighing the Evidence. *NEJM* 2007;357:64-6.
11. Jeffrey MD, Stephen M, Gregory DC. Rosiglitazone- Continued Uncertainty about safety. *NEJM* 2007;357:63-4.
12. Leiter LA. Beta-cell preservation: a potential role for thiazolidinediones to improve clinical care in type 2 diabetes. *Diabet Med* 2005;22:963-72.
13. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005;294:2581-6.
14. Clifford J. Rosen, M.D. The Rosiglitazone Story — Lessons from an FDA Advisory Committee Meeting Published at www.nejm.org August 8, 2007(10.1056/NEJMp078167).