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Editorial

Training and making of a surgeon - with the mind and not the eye !!

Dr. Chintamani

Training as a surgeon is the most exciting and happening part of a surgeon's story. The journey, that is surgery, makes surgeon and his job very special and unique. To trace it back to the days when surgery was considered the "queen" of all specializations in medicine and "surgeon" the gentleman with the heart of a lion and eyes of a hawk, training has undergone a drastic but not necessarily a positive change. There is an interesting Chinese story that in a way sums up the essence of training as a surgeon. With more and more industry driven and technology dependent "developments" happening, surgery has become more and more complicated and we have made simple things more cumbersome. The surgeons today see more with their eyes rather than with their minds.

The story of a Chinese emperor and his cook has been around for some time and has been used for explaining the significance of seeing with the mind .The emperor was looking down from his sitting room in to the courtyard where his cook was busy chopping a bullock for the dinner. Each stroke appeared calculated and meticulous, the axe finding the crevices and spaces in between the joints with ease, perfection and finesse. The entire exercise was appearing like a well co-ordinated orchestra producing a soothing symphony. The emperor was very thrilled and impressed and called for the cook. The cook was very scared and flabbergasted to face the emperor for the first time in his life.

What makes you chop the bullock with such perfection, and with the ease of a master? The cook narrated his story, great emperor! When I started learning this art at the feet of my father, it I would see bullocks all around and would change my axe every three days. Gradually, as my learning continued I started seeing just the bullock and would change my axe once in two or three months. With the passing weeks I did not even have to look at the bullock and would find the crevices with ease and my axe would be changed annually. Now I do not see the bullock at all and would find the boneless planes without discomfort, I do not have to see the bullock with my eyes anymore and this axe has been with me for more than a decade. I now see with my mind and not the eye.

There is no short cut to making of a surgeon; the mentor and the mentee have to be in close and selfless spiritual and professional contact for an optimum duration. Both have to excel and work for each other's excellence. Does not matter how far we go in creating a robot slave, human beings and human values only, would make a surgeon. "A fool with a tool is still a fool". It has been amply demonstrated in many studies that the evolution of gadgetteries have only made a mediocre surgeon appear acceptable, excellence still rules and would do so in future too. To excel is the true freedom that we all strive for, knowingly and unknowingly and a great achiever is known not by where he has reached but the obstacles he has overcome. Hard work therefore is the key to excellence and training of a surgeon should take him from eyes to the mind.

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Clinical profile of peritonitis

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IN BRIEF

This study was undertaken as peritonitis is one of the common surgical emergencies all over the world. However the mode of onset, etiological factors, morbidity and mortality will differ; depending upon available facilities for diagnosis, literacy status of the population, socio-economic status and religious notions., India is still developing country. The ignorance, illiteracy still persist all over the country which plays role in everyones life., The S.S.I.M.S & R.C, Davangere has got all kinds of cases of peritonitis presenting the sectional study of this country. All aspects of peritonitis have been considered in detail such as age and sex incidence, mode of onset, etiological factors, morbidity and mortality so as to fullfil all criteries of scientific study.

Key words: Peritonitis, Incidence

Introduction

Peritonitis continues to be one of the major problems confronting surgeons. Despite many advances in antimicrobial agents, early diagnosis, better understanding of fluid and electrolyte imbalance, refined surgical techniques, mortality from diffuse suppurative peritonitis continues to remain high[1].

The resolution or persistence of infection is mainly due to; polymicrobial nature of peritonitis, microbial interaction with host defence, the anatomy and defence capabilities of the peritoneal cavity and possible infection potentiating agents in the peritoneal cavity[2].

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This study was undertaken to find out the age and sex incidence, various etiological factors and the outcome of surgery.

Materials and Methods

Clinical profile of peritonitis was studied from January 2009 to January 2010. Total of 50 cases of peritonitis are included in the present study. These patients were admitted and managed in S.S.I M S & R.C Davangere. All cases of peritonitis admitted during above said period were considered and were taken randomally. Every case of peritonitis was examined, investigated and diagnosed as shown in

The erect abdominal X-ray was taken for gas under diaphragm, ground glass appearance and multiple air fluid levels. The ultrasonography abdomen and pelvis was done to reveal type of peritoneal content (fluid or pus) and also to identify biliary conditions like acute cholecystitis which mimic perforated ulcer.

The diagnostic peritoneal tap was done and the fluid was sent for culture sensitivity. CT-scan used in patient with head injuries or on corticosteroids, in whom abdominal examination may be equivocal unreliable, but is not necessary in clearly evident peritonitis.

Table 1

General examination and investigation	Number of cases	
	Present/Positive	Absent/Negative
Fever	24	26
Tachycardia	28	22
Distension (abdomen)	38	12
Guarding	30	20
Rebound tenderness	42	8
Liver dullness	28	22
Peristaltic sound	19	31
Rectal tenderness	26	24
Chest infection	10	40
TC>10,000cells/mm3	30	20
Gas under diaphragm	30	20
Paracentesis(abdomen)	36	14
C/S of peritoneal fluid	34	16

The following graph shows age incidence of peritonitis in 50 cases.

The primary objectives in the treatment of peritonitis are; resuscitation, initiation of antibiotics, elimination of the source of bacterial contamination, reduction of the bacterial inoculums and continued metabolic support.

All patients were kept nil orally and dehydration was corrected by intravenous Ringer lactate and 5% Dextrose saline.

The shock was corrected by Haemaceal or Blood transfusion. To keep stomach empty Ryle's tube aspiration was done second hourly. All patients were given antibiotics pre-operatively.

Table-2 shows aetiology of peritonitis in 50 cases

The patient was taken up for surgery once general condition was improved. All cases were operated by single experienced surgeon.

The patient under general anaesthesia, the abdomen was opened by right or midline incision. The abdominal visceras were inspected, the peritoneal fluid collected, measured and sent for culture and sensitivity. The site of pathology was identified and surgical procedure done accordingly. The peritoneal lavage was given by using normal saline till returning fluid becomes clear. In this

Table 2: Shows aetiology of peritonitis in 50 cases

Aetiology of Peritonitis	Number of cases	Percentage
Primary peritonitis	2	4%
Gastric perforation	3	6%
Duodenal perforation	20	40%
Jejunal perforation	1	2%
Stomal perforation	2	4%
Ileal perforation	12	24%
Appendicular perforation	3	6%
Sigmoid volvulus with perforation	1	2%
Intestinal obstruction with strangulation	3	6%
Uterine perforation	2	4%
Necrotizing enterocolitis	1	2%
TOTAL	50	100%

study no antibiotics were used for peritoneal lavage.

Operative management primarily should be directed towards the control of the source of contamination, which can be achieved by closure of perforation by using No-1 vicryl with omental patch, resection and end to end anastamosis in multiple perforations, removal of organ and peritoneal drains alone in inoperable cases.

The reduction of bacterial inoculums in order to prevent recurrent sepsis can be achieved by swabbing and debriding fibrin, blood and necrotic material from the peritoneum. Peritoneal irrigation to decrease the incidence of wound infection. Following major part of surgery single or double peritoneal drain was kept in all cases by using tube drain.

The abdominal incision was closed by using No-1 vicryl in layers. Tension sutures were used in few cases of diffuse peritonitis. All patients were closely observed post-operatively, mainly for general condition, distension of abdomen, amount of peritoneal fluid drained and Ryle's tube aspiration.

All patients were kept nil orally post-operatively till good peristalitic sounds heard. The antibiotics were continued depending upon the severity mainly cephalosporins.

All complications of a severe bacterial infection and post-operative complications of an abdominal surgery are possible, of those respiratory complications predominate. But the special complications of peritonitis are paralytic ileus, intestinal obstruction due to peritoneal adhesions, residual abscesses and burst abdomen.

Table- 4 shows mortality in different groups.

Table 3: Shows culture sensitivity in 50 cases.

Name of organisms	Number of times grown on culture	Percentage	Antibiotics	Sensitive to number of isolates
. Coli	18	36%	Amikacin	15
K.Pneumoniae	6	12%	Cefotaxim	16
Staph. Aureus	5	10%	Gentamycin	10
Citrobacter	2	4%	Ciprofloxacin	10
Pseudomonas	2	4%	Netromycin	4
Proteus	1	2%	Ampicillin	12
Negative	16	32%	Resistant to all	8

Discussion

The peritonitis is one of the common surgical emergency throughout the world and is also common cause of acute abdomen. It accounts for about 20% of acute abdomen. When the term peritonitis is used without qualification, it always implies bacterial peritonitis, usually both aerobic and anaerobic organisms. The blood borne infection results in primary peritonitis, the incidence of which has decreased from 10% to 2% in children and adults due to early diagnosis, improved antibiotics agents and literacy of the population[3,4].

The incidence of secondary peritonitis is increasing compared to the primary peritonitis due to consumption of spicy food, NSAIDS, alcohol and increased incidence of enteric fever and resistant organisms. The reduction in mortality from 90% to 10%-20% today not only depends upon the surgical intervention, is also due to the armamentarium of effective antibiotics, knowledge regarding fluid and electrolyte balance, pre and post-operative care of the patient[5]. Despite these advances, mortality persists, with patients succumbing to the effects of sepsis and eventual multisystem failure (6). The single most influential factor in the successful management is early, accurate diagnosis and treatment.

Table 4

Cause of peritonitis	Number of cases affected	Number of deaths	Percentage
Primary peritonitis	2	2	100.00%
Gastric perforation	3	1	33.33%
Duodenal perforation	20	2	10.00%
Ileal perforation	12	3	25.00%
Uterine perforation	2	1	50.00%
Jejunal perforation	1	0	------
Stomal perforation	2	0	------
Appendicular perforation	3	0	------
Intestinal obstruction & strangulation	3	1	33.33%
Sigmoid volvulus & perforation	1	0	------
Necrotising enterocolitis	1	1	100.00%

In the present study of 50cases of peritonitis, the maximum incidence was found between 20-40years (58%) of age. The youngest was of 3years and eldest was of 80years, with high incidence in the middle age. In our country the ileal perforation secondary to enteric fever is common in young adults but we have come across the same condition in 3year old child[7].The age incidence of our study fit with age incidence of Illingworth, Glasgow series. Peritonitis can occur at any age group but has different etiological factors.

The present study showed male predominance (74%) with Male: Female ratio of 2.8:1. This is because of increased intake of spicy food, smoking and alcohol consumption in male and stress and strain in female patients [8,11].

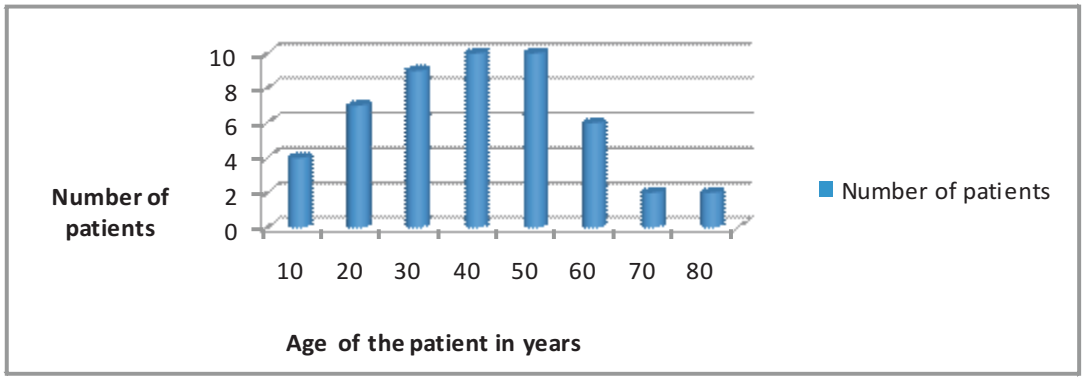
The history of fever in 24patients (48%) and common who presented late in whom ileal perforation was suspected. The history of consumption of NSAID's in 12patients (24%) which plays an important role in peptic ulcer perforation. It is well documented that drugs like aspirin and corticosteroids cause peptic ulceration and also perforation. These drugs damage the mucosal protective mechanisms and are said to possess anti-healing factors[9].

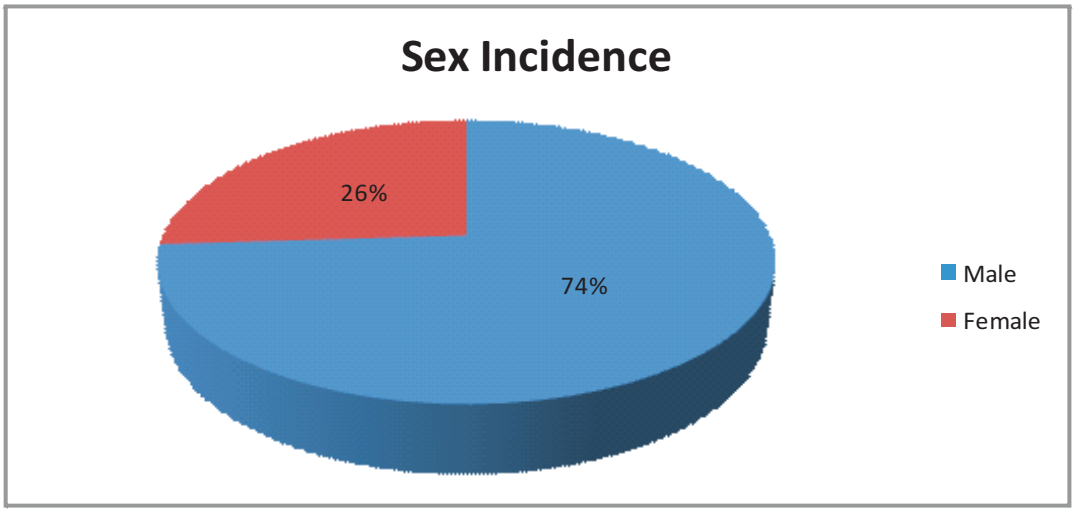
Most of our patients were found anaemic. The total count was ranging from 4,400cells/mm3 to 16,000cells/mm3 with mean of 10,200cells/mm3. The total count was less in gastric and duodenal perforations. After few hours of peritonitis the peritoneal fluid becomes turbid, as it contains leukocytes, proteins, cellular debris, fibrin sheets and blood[10].

The evidence of perforation that is free gas under the diaphragm was present in 30cases (60%), ground glass appearance in 5cases and multiple fluid level in 5cases. No abnormality detected in 10cases on X-ray. The gas under diaphragm is one of the most reliable diagnostic procedure in an acute perforated peptic ulcer[12,13]. However, this investigation may not be possible in patients with poor general condition. This procedure has its own limitation viz absence of gas under diaphragm may be due to dry perforation or absorption of gas. Absence of gas will not rule out perforation[14].

The abdominal paracentesis was performed in all cases, it was positive in 36cases (72%) and negative in 14 cases (28%). The paracentesis may become positive when there is large amount of free fluid in the peritoneum. However negative paracentesis will not rule out the peritonitis[15].

This procedure is done easily and safely with slightest discomfort to the patient and much information is gained. Positive tap is of significance[16]. The aspirate is bile stained in peptic perforation, turbid in ileal and appendicular perforation, blood stained in





blunt trauma abdomen and perforation of malignant growth.

In our study most of the aspirate was turbid, in 3 cases it was blood stained, 2cases of ileal perforation secondary to blunt trauma and one case of perforated uterine growth. Nevertheless nothing much is lost by doing an abdominal paracentesis. In 14cases, it ended in dry tap, could be due to small quantity of fluid or early sealing of perforation by omentum. No complications such as haematoma or injury to bowel in any of the cases following paracentesis.

The biopsy from the ulcer edge was taken in all 3 cases of gastric ulcer perforation, were benign. The biopsy is essential for early diagnosis and treatment of malignancy. Those from ileal perforation; 8 cases were enteric and 4 cases were non-specific.

The peritoneal fluid was sent for culture and sensitivity in all 50 cases. In 34 cases organisms were isolated and in 16 cases no organisms isolated. E.Coli being the commonest in 18 cases(26%) and Klebsiella pneumonia in 6 cases(16%)[17,18].

Conservative treatment in 2 cases and laparotomy in 48 cases, showed improvement in 8-10hrs[19]. The duodenal perforation was common aetiology of peritonitis followed by ileal perforation. The surgical procedure carried out was simple closure in few cases and omental patch in few cases, resection and end to end anastomosis in 4 cases. None of the patient treated with definitive surgery ie vagotomy and drainage procedure.

In our study intra-operative antibiotic lavage was not done in any cases. The peritoneal lavage done with normal saline in all cases which were treated surgically. The single or double peritoneal drain was kept[11, 20,21].

The commonest post-operative complications encountered were superficial gaping in 8cases(16%), pneumonitis in 4

cases(8%), stitch abscess in 3 cases(6%), complete dehiscence in 2 cases(4%)[11,24].

In all cases, history of illness was ranged from 2hours to 4days. 20 cases presented in 0-8hours, 18 cases between 8-48hours and 12 cases 48-96hours. The pain was constant symptom and was confined to upper abdomen in early cases and become generalised later period. The time interval between the symptoms and admission as well as between admission and surgery plays an important role in the management, incidence of morbidity and mortality[22].

It is shown that definitive surgery in cases of more than 12 hours delay carries high mortality rate, not only delay after perforation, but also the poor general condition of the patient and gross contamination of peritoneal cavity.

The overall mortality rate in our study was 22%, it was 16% in operated cases[11,21,23]. The mortality was found to be increased in elderly patient, late presentation, gross peritoneal contamination, assosciated systemic diseases. The reduced mortality rate is due to better availability of antibiotics, better anaesthetic care and better pre and post-operative care.

Conclusion

Peritonitis is a well recognised intra-abdominal infection throughout the history of medicine. It is morbid clinical manifestation which is of concern to both the surgeon and the patient. Peritonitis can occur in all age groups and both sexes. Majority of the cases can be diagnosed with detailed history and clinical examination alone. The abdominal paracentesis as a bed side procedure and plain X-ray abdomen were important diagnostic tools to confirm the diagnosis. The treatment is exclusively exploratory laparotomy. If the condition is diagnosed and treated early, the morbidity and mortality can be reduced to considerable extent.

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Role of low hemoglobin level in predicting response to neoadjuvant chemotherapy in breast cancer and its correlation with p53, bcl-2 and VEGF – a prospective clinical study

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IN BRIEF

Neo-adjuvant chemotherapy (NACT) is an integral part of multi-modality approach in the management of locally advanced breast cancer (LABC). It is required both for the local control (to ensure microscopically free margins during surgery) and distant or systemic control [1-6]. Development of resistance to chemotherapeutic agents is a major and evolving problem. Various markers like P-Glycoprotein, tumor suppressor gene p53, apoptotic markers(Bcl-2, Bax) have been studied to predict the response to NACT[1].

Key words: Hemoglobin, breast cancer, neoadjuvant, chemotherapy

Introduction

Few studies suggest that the response to cyclophsphamide which is a highly oxygen dependent cytotoxic drug is dependent on Hemoglobin level[7-9]. The prognostic impact of anemia in cervical cancers is well established. In a recent meta-analysis, anemia was found to be an independent prognostic factor for increased death rates in various solid tumors (head and neck, lung, prostate) and lymphoma[7].The relation between low Hb levels and a low oxygenation status of malignant tissues could be demonstrated in several studies[10,11,12,13,14]. Tumor hypoxia is a direct consequence of structural abnormalities of the microvasculature and functional impairments of the microcirculation and results from either limited pO2 diffusion (chronic hypoxia) or limited perfusion (acute hypoxia)[11]. Singer et al demonstrated with breast cancer cell lines that diminished mitochondrial energy generation (due to tumor hypoxia) was related to malignant progression[15,16].

Poor oxygenation of residual and accelerated repopulating tumor cells may have severe effects on tumor cell biology. Hypoxia is one of the reason for genetic instability and the development of mutations in malignant tissues[10,17,18]. Such mutations could affect genes encoding for apoptotic cell death. An example of such a gene is p53 tumor suppressor gene, which induces apoptosis in hypoxic tumor cells. Genetic alterations promoted by hypoxia could result in mutant p53 i.e a loss of functional p53 tumor suppressor gene and therefore in a loss of apoptotic potential in hypoxic tumor cells[10,19]. Another form of genetic alteration in hypoxic tumor cells is overexpression of the apoptosis inhibitor protein Bcl-2. According to Graeber et al. an overexpression of this protein could be demonstrated especially in hypoxic tumor cells[10,19].

Normal breast development is controlled by a balance between cell proliferation and apoptosis, and there is strong evidence that

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tumor growth is not just a result of uncontrolled proliferation but also of reduced apoptosis[20]. A large number of anti-cancer agents with widely differing modes of action have been demonstrated to induce apoptosis in vitro, suggesting this as a significant final common pathway for exerting their clinical effects. Mechanisms that suppress apoptosis may be important in the development of intrinsic and acquired resistance to cytotoxic drugs[1,4].

Hypoxia of tumor cells is the most stimulating factor for release of vascular endothelial growth factor[10,17]. VEGF is the most important molecule for angiogenesis[10,17]. In consequence, hypoxic malignant tissue could more rapidly develop a sufficient vascularisation than normoxic tumors. Angiogenesis is necessary for the growth and invasiveness of primary tumors and is integral part of cascade of biologic events involved in tumor metastasis[21].

One of the major problem with NACT is chemoresistance. It is therefore vital to assess the response to NACT in order to tailor regime for a particular patient to predict the chemoresistance[1]. The clinical response along with complete pathological response is still considered a surrogate marker of response against which all other predictive markers are compared. Various markers like P-Glycoprotein, tumor suppressor gene p53, apoptotic markers(Bcl-2, Bax) have been studied to predict the response to NACT. The need to have a reliable and inexpensive predictor of response in third world scenario can not be overemphasized since majority of patients present late and the resources are limited and scarce.

Low hemoglobin level causes hypoxia in tumor cells, which in turn reduces apoptosis by causing genomic instability i.e overexpression of anti apoptotic gene Bcl-2 and decreased expression of functional tumor suppressor gene p53. Tumor hypoxia also causes increased angiogenesis and thus increased expression of VEGF. Low hemoglobin level, therefore may be utilized as a cost effective and reliable predictor of response to NACT. Against this background a prospective study was contemplated with following aims and objectives;

1. To correlate hemoglobin level with tumor suppressor gene p53, apoptotic inhibitor Bcl-2 and vascular endothelial growth factor VEGF.
2. To correlate expression of tumor suppressor gene p53, apoptotic inhibitor Bcl-2 and vascular endothelial growth factor with response to neoadjuvant chemotherapy.
3. To ascertain whether the low hemoglobin level could be utilized as a reliable predictor of response to neoadjuvant chemotherapy.

Methods

152 FNAC proven cases of locally advanced breast carcinoma according to AJCC (American Joint Committee On Cancer) classification were included in the study.

A thorough clinical and ultrasonographic examination (USG) of all the patients including the opposite breast was performed to stage the disease accurately. A core biopsy using a tru-cut needle was performed for immuno-histochemical estimation of the apoptotic inhibitor i.e. Bcl-2, tumor suppressor gene p53 and vascular endothelial growth factor (VEGF) before initiating the chemotherapy. Routine and metastatic work up was done including complete blood examination (total blood count including hemoglobin level, platelet count), chest radiograph, ECG (Echocardiography when ECG had a positive finding), liver function tests, Bone Scan, USG abdomen, KFT (Kidney function tests).

Patients were subjected to three cycles of FAC regime containing cyclophosphamide , adriamycin , 5-fluorouracil at an interval of three weeks. Before each cycle the patients were clinically and sonologically examined for the breast tumor size, axillary lymph node status & appearance of systemic metastasis. Patey's modified radical mastectomy was performed three weeks after the last cycle and the mastectomy specimen was examined for pathological response, resected margins,

axillary lymph nodes, Bcl-2, p53 and VEGF expression(post NACT).

On the basis of Hb level patients were divided into two groups. Those with Hb level less than or equal to 11 g/dl were included in low Hb group (anemic), while those with more than 11 g/dl were included in normal Hb group(non anemic).

The pathological tumor response was evaluated by size measurement at the time of tumor resection macroscopically and by detecting tumor cell existence (or not) microscopically.

Clinical responders

Were defined as patients with a complete (CR) or partial response (PR) [CR: complete resolution of tumor, PR>50% regression in maximum diameter of initial tumor] after 3 cycles of NACT. Non-responders were patients with a minimal response (MR<50% regression in maximum diameter of initial tumor), no change (NC) or local progression. Pathological complete response (pCR) was defined as absence of any gross or microscopic evidence of residual tumor in the mastectomy specimen i.e. absence of residual invasive or in situ disease following NACT. Its assessment was done irrespective of the clinical response status. Clinical response was taken into consideration for statistical analysis as the pCR was observed in only 20(19%) patients(n=105).

Immunohistochemical methods

Methods for antigen retrieval

Biopsy specimen was preserved in buffered formalin solution. Five-micron sections were prepared from paraffin embedded blocks on poly-l-lysine coated glass slides. Sections were deparaffinized in xylene for 15 minutes and hydrated in alcohol for 15 minutes. Further, incubation was done in 0.3% hydrogen peroxide in methanol solution for 45 min. The slides were washed with citrate buffer and kept in a water bath at 90–95°C for 45 minutes for antigen retrieval.

Methods FOR BCL-2 expression

Sections were washed with Tris buffer saline (TBS) solution and incubated with blocking antibodies (DAKO monoclonal mouse antihuman Bcl-2 oncoprotein for Bcl-2 expression) at 37°C. Sections were washed with TBS solution. Incubation with avidin-biotin complex (ABC) was done at 37°C for one hour and washed with TBS solution. 3,3 Diaminobenzidine tetra hydrochloride solution applied for 3–5 min. Counter-staining with haemotoxylin solution done for 3–5 min. Sections were washed with distilled water, air dried and mounted using DPX mountant.

Methods for P53 and VEGF expression

Sections were washed with Tris buffer saline (TBS) solution and incubated with blocking antibodies (Santa cruz monoclonal mouse antihuman p53 antibody for p53 expression and monoclonal VEGF antibody for VEGF expression) at 4°C overnight. Incubation with biotinylated secondary antibody was done at 37°C for 45 minutes. Incubation with streptavidin-HRP conjugate was done for another 45 minutes[3,3]. Diaminobenzidine tetra hydrochloride solution applied for 3–5 min. Counter-staining with haemotoxylin solution done for 3–5 min. Sections were washed with distilled water, air dried and mounted using DPX mountant.

For Bcl-2, positive controls were the mantle zone of lymphoid follicles, for p53 the positive controls were normal breast cancer tissue and for VEGF the positive controls were normal placental tissue . The negative controls for Bcl-2, p53 and VEGF were the test slides without primary antibody.

The pattern of positive staining for bcl-2 and VEGF was cytoplasmic.

The pattern of positive staining for p53 was nuclear.

The primary antibody for bcl-2 was procured from DAKO.

The primary antibody for p53 and VEGF were procured from Santa cruz.

Bcl-2 Monoclonal Mouse Anti-Human code no. M 0887.

Code no. for p53 was (DO-1)sc126.

Code no. for VEGF was A 20 sc152.

Dilution for Bcl-2 was 1:40, for p53 1:50 while for VEGF dilution was 1:100.

The results were interpreted on the basis of following criteria:

Percentage of cells showing immune bodies; <10%: score = 0, 10–25%: score = 1, 25–50%: score = 2, >50%: score = 3

Score 0 and 1 were taken as negative results while score 2 and 3 were taken as positive.

The intensity of staining was also assessed and it was found that staining intensity correlated closely with percentage of positive cells showing immune bodies and a single index i.e. percentage of positive cells was used for analysis.

Statistics

Descriptive studies were performed with SPSS version 10. The significance of response assessed using paired t-test. Significance of correlation between various variables assessed using chi-square test and coefficient of correlation was calculated by Pearson correlation coefficient.

Results

152 patients of LABC were included in the study with mean age being 45.36 years (range 26-65 years) and 80 (52.6%) patients were premenopausal. The mean tumor size before NACT was 7.24 cm. 61 patients had N1 disease, 81 patients presented with N2 disease while 10 patients had N3 disease in the axilla.

The clinical response was assessed using stringent World Health Organization (WHO) criteria and reduction in mean tumor size after three cycles of NACT was found to be statistically significant ($p < 0.05$). 105 patients (69%) patients (n = 152) were responders [*complete response in 20 and partial response in 85 patients (n =105)*] while the rest 47(30.9%) were non-responders.

Significant clinical response was observed in the axillary lymph node status after NACT. Of 61 N1 patients 38(62.2%) patients showed complete response i.e. they were down staged to N0, 14(22.9) patients remained N1, while 9(14.7%) patients progressed to N2 disease. Amongst the patients with N2 disease (n = 81), 20(24.6%) were downstaged to N0, 32(39.5%) patients were downstaged to N1, 27(33.3%) patients remained N2 ,while 2(2.4%) patients progressed to N3. Of N3 patients (N=10), 9(90%) patients were downstaged, 6(60%) to N2 and 3(30%) to N1, while 1(10%) patient remained N3. This downstaging in the axillary lymph node status was found to be statistically significant ($p < 0.05$).

The clinical response however did not have any significant correlation with the pre NACT tumor size, age and menopausal status of the patients.

In our study 56 (36.8%) patients were in low Hb group, while 96 (63.1%) patients were in normal Hb group. It was observed that of 56 anemic patients 38 patients (67.8%) were nonresponders and 18 (32.1%) were responders, while of 96 nonanemic patients, 87 (90.6%) patients were responders and 9 (9.3%) were nonresponders. Thus a statistically significant correlation was observed between anemia and poor clinical response.($p<0.05$)

In the biopsy specimen before initiation of NACT , 57 (37.5%) patients were p53 +ve and 95 (62.5%) were –ve. Immunohistochemistry was also done for Bcl-2 and VEGF and it was observed that 52(34.2%) patients were Bcl-2 positive and 54(32.8%) patients were VEGF positive.

Tumor suppressor gene P53, anemia and clinical response

It was observed that of 57 p53 +ve patients 41(71.9%) were nonresponders and 16(28%) were responders. While of 95 p53 –ve patients 89(93.6)% patients showed response and 6(6.4%) were nonresponders. And this correlation between p53 positivity and poor clinical response was statistically significant.($p<0.05$)

Of 56 anemic patients, 45(80.3%) were p53 +ve and 11(19.6%) were –ve. While of 96 nonanemic patients only 12 (12.5%) were p53 +ve.Thus a statistically significant correlation was observed between low Hb level and high p53 expression.($p<0.05$)

It was also observed that of 45 p53 +ve anemic patients 36(80%) were nonresponders and 9(20%) were responders. Thus a significant correlation was observed between anemia, p53 positivity and poor response.($p<0.05$)

BCL-2, anemia and clinical response

Of 52 Bcl-2 +ve patients only 9(17.3%) were responders and 43(82.6%) were nonresponders. While of 100 Bcl-2 –ve patients 96 (96%) were responders and 4(4%) were nonresponders. This correlation between positive Bcl-2 expression and poor clinical response was statistically significant.($p<0.05$)

Of 56 anemic patients, 42(75%) were Bcl-2 positive and 14(25%)were Bcl-2 negative. While of 96 nonanemic patients only 10(10.4%) were Bcl-2 +ve. Thus a statistically significant correlation was observed between low Hb level and high Bcl-2 expression.($p<0.05$)

It was observed that of 42 Bcl-2 +ve anemic patients, 37 (88%) were nonresponders and 5(11.9%) were responders. Thus a significant correlation was observed between anemia, Bcl-2 positivity and poor response.($p<0.05$)

VEGF, anemia and clinical response

Of 54 VEGF +ve patients, 45 (83.3%) were nonresponders and 9 (16.6%)were responders, while of 98 VEGF –ve patients, 2(2%) patients were nonresponders and 96 (97.9%) were responders. This correlation between positive VEGF expression and poor clinical response was statistically significant.($p<0.05$)

Of 56 anemic patients 44(78.6%) were VEGF +ve and 12 (21.4%) were VEGF –ve. While of 96 nonanemic patients 10(10.4%) were VEGF +ve. Thus a statistically significant correlation was observed between low Hb level and high VEGF expression.($p<0.05$)

It was observed that of 44 VEGF +ve anemic patients, 39(88.6%) were nonresponders and 5(11.3%) were responders. Thus a significant correlation was observed between anemia, VEGF positivity and poor response.($p<0.05$)

Discussion

Breast cancer is the commonest malignancy in women worldwide and more than 1,000,000 new cases are diagnosed every year[20,21]. Although the incidence has increased over last 20 years, the prognosis has improved, partly because of early diagnosis and as a result of more active treatment against systemic spread[21].

Carcinoma of breast is a leading cause of cancer mortality in women all over the world and the second most common malignancy in India after carcinoma of the uterine cervix[1,23-26]. In India like in other developing countries 25–30% cases are locally advanced at the time of diagnosis[1,23-26]. The recommended approach for the management of LABC is a multimodality approach intended to provide both local and systemic control and studies have confirmed that surgery alone is an inadequate treatment[23,26]. The realization that patients with LABC are likely to have undetectable micro metastases at diagnosis has lead to systemic treatment assuming an important role, as even aggressive surgical techniques do not reduce the higher incidence of local recurrence. Most importantly surgery does not change the pattern of distant failure in these patients as they often have micrometastatic disease at the time of diagnosis[23].

Neoadjuvant chemotherapy was first introduced with a 70% objective response rate in 1970s and was initially utilized to convert unresectable tumors to smaller tumors making them more amenable to local control with either surgery or radiotherapy. Although the correlation between the tumor response and prognosis is still uncertain, it is generally believed that such a relationship may exist[23,25]. The other important advantage of NACT is

that it provides an *in vivo* chemosensitivity test for assessment of tumor response from which prognostic information could be obtained.

Apoptosis

Normal breast development is controlled by a balance between cell proliferation and apoptosis, and there is strong evidence that tumour growth is not just a result of uncontrolled proliferation but also of reduced apoptosis[20].

Apoptosis is a closely regulated form of active cell death defined by characteristic biochemical and morphological criteria. A large number of anti-cancer agents with widely differing modes of action have been demonstrated to induce apoptosis in vitro, suggesting this as a significant final common pathway for exerting their clinical effects. Mechanisms that suppress apoptosis may be important in the development of intrinsic and acquired resistance to cytotoxic drugs[1,4].

Apoptosis is a regulated phenomenon capable of being inhibited and activated. Indeed there is evidence that stimulation of some cells by trophic cytokines or increase in their levels of expression of Bcl-2 proto-oncogeny can greatly increase their resistance to the apoptosis-inducing effects of anticancer drugs. Thus Bcl-2 proto-oncogeny expression may be implicated in the development of resistance of tumors to therapeutic agents and may contribute to tumor growth and perhaps to oncogenesis by allowing the inappropriate survival of cells with DNA abnormalities[1,27].

Deregulated expression of the Bcl-2 protein represents the best-known example of a potent blocker of apoptosis. Over expression of Bcl-2 has now been shown to protect a wide variety of cell types from induction of apoptosis by many different anticancer agents[1,4].

The other marker which is studied extensively in breast cancer is tumor suppressor gene ,p53. The protein product of p53 controls cellular functions involved in apoptosis, the cell cycle, and the repair of DNA.[20,28] Mutations in this gene are the most common mutational event in cancer. Mutations in the gene or increased expression of the p53 protein (an indirect marker of mutation as this often results in stabilisation of the protein), has been associated with a poor prognosis to breast cancer in some studies[20,29]. Those studies that have measured mutation as opposed to protein over expression have consistently shown that mutated p53 is related to a poor response to chemotherapy.[20,30]

Anemia and tumor hypoxia

Anemia is a major problem worldwide , more so in developing countries[7]. The prognostic impact of anemia in cervical cancers is well established. In a recent meta-analysis, anemia was found to be an independent prognostic factor for increased death rates also in various solid tumors(head and neck, lung, prostate) as well as lymphoma[7]. It is been seen in studies that there is not a linear relationship between Hb level and local failure rates or survival[7]. Hb levels in the normal or nearly normal range do not correlate with failure rate[7]. Evans and Bergsjo have demonstrated that patients with Hb level of less than 11 gm/dl had a significantly poorer overall survival as compared with patients with Hb level of 11g/dl or more.[7,33] The relation between low Hb levels and a low oxygenation status of malignanttissues could be demonstrated in several studies[10-14]. Tumor hypoxia is a direct consequence of structural abnormalities of the microvasculature and functional impairments of the microcirculation and results from either limited pO2 diffusion (chronic hypoxia) or limited perfusion (acute hypoxia)[11]. Studies suggest that tumors respond more sensitively to a lower Hb concentration than normal tissues. A possible explanation for this phenomenon could be that the inadequate vascular structure in malignant tissue is not able to compensate for the deficiency of oxygen carriers with a decreased vascular resistance and enhanced flow[11].

Effect of tumor hypoxia on apoptosis

Poor oxygenation of residual and accelerated repopulating tumor cells may have severe effects on tumor cell biology. Hypoxia is one of the reason for genetic instability and

the development of mutations in malignant tissues[10,17,18]. Such mutations could affect genes encoding for apoptotic cell death. An example of such a gene is p53 tumor suppressor gene, which induces apoptosis in hypoxic tumor cells. Genetic alterations promoted by hypoxia could result in a loss of functional p53 tumor suppressor gene and therefore in a loss of apoptotic potential in hypoxic tumor cells[10,19]. In vitro studies demonstrated that repeated hypoxic exposure resulted in overgrowth of mutant p53 clone i.e decrease in functional p53.[31]

Another form of of genetic alteration in hypoxic tumor cells is overexpression of the apoptosis inhibitor protein Bcl-2. According to Graeber et al. an overexpression of this protein could be demonstrated especially in hypoxic tumor cells[10,19].

Angiogenesis

One very important prognostic indicator which is widely studied for breast cancer is angiogenesis. Angiogenesis is necessary for the growth and invasiveness of primary tumors and is integral part of cascade of biologic events involved in tumor metastasis[21]. The mechanisms by which neovascularisation stimulates tumor progression are as follows:

1) delivery of nutrients and oxygen necessary for tumor cells to grow(perfusion effect).

2) facilitation of penetration of tumor cells through vessel wall and their transport to distant organs(metastatic effect).

3) secretion of some cytokines (IL 1-6 and 8) and growth factors(G-CSF, TGF-beta-1, IGF and angiogenic peptides) from endothelial cells that directly stimulate tumor cells(paracrine effect). The switch to angiogenic phenotype may be due to the overexpression of number of endothelial growth factors and/or to reduced expression of endogenous angiogenesis inhibitors[21].

Vascular endothelial growth factor, also known as vascular permeability factor, is a potent and widely distributed angiogenic peptide.[21] VEGF is a heparin-binding glycoprotein that has several important effects on vascular endothelial cells. Currently VEGF is considered to be most selective mitogen for endothelial cells.[32] VEGFs are polyfunctional molecules that have been implicated in vasculogenesis, endothelial cell proliferation and migration, vascular permeability and stromal degradation through activation of some proteolytic enzymes involved in tumor invasiveness and angiogenesis.[21] VEGF expression is increased in response to various stimuli, including certain oncogene products e.g mutant ras[21]; and overexpression of transforming growth factor- alpha[21]; and hypoxia[21].

The most stimulating factor for release of VEGF is hypoxia in surrounding tumor cells[10,17]. In consequence, hypoxic malignant tissue could more rapidly develop a sufficient vascularisation than normoxic tumors. For microscopic residual cells under hypoxic conditions this means that they attain a sufficient blood supply by the release of VEGF much faster than normoxic residual tumor cells. A relapse of disease and regrowth of tumor tissue therefore is more likely in patients with low Hb levels[10,17].

There seems to exists a threshold in the range of about 11 g/dl below which the prognosis dramatically worsens[7]. the presence of such a threshold has also been demonstrated by by Evans and Bergsjo[7,33]. Based on these observations we divided the patients in two groubs taking Hb level 11 g/dl as the cut off value.

In our study we could not find any relation between clinical response and patient age, pre NACT tumor size, menopausal status.

In this prospective clinical study it was observed that patients of LABC with pretreatment low Hb level have poor clinical response to NACT, while nonanemic patients have good response to NACT. 67.8% of anemic patients were nonresponders, while 90.6% of nonanemic patients were responders to NACT.

In our study it was observed that anemic patients have increased expression of mutant tumor suppressor gene p53 (i.e nonfunctional p53), Bcl-2 and VEGF. Increased expression

of p53 and Bcl-2 lead to decreased apoptotic cell death (the mechanism responsible for chemotherapy induced tumor cell death) and thus chemoresistance. Overexpression of VEGF leads to increased angiogenesis and thus increased tumor invasiveness. This increase in angiogenesis also leads to chemoresistance.

Correction of Hb level before NACT can avoid chemoresistance. Correction can be done with blood transfusions and erythropoietin along with hematinics[8].

Conclusions

This study highlights the importance of hemoglobin level in predicting response to NACT in breast cancer patients. While many biological markers are in use and many are under trial to tailor the chemotherapy for a particular patient, most of these markers including apoptotic markers or p-glycoprotein etc. are not very frequently available and are expensive for a third world cancer set up. Patients with low Hb level before initiation of NACT were found to be poor clinical responders. Pretreatment low Hb level may thus be utilized as a predictor of response to NACT and thus correction of Hb should be done before initiation of treatment in order to avoid chemoresistance.

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Gastrointestinal stromal tumors (GIST): A Pathologist's Viewpoint

Jain Ila

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors that arise from the intestinal cells of Cajal, the gut pacemaker cells [1,2]. They are the most common sarcoma of the gastrointestinal tract, representing 0.2% of all GI tumors. The usual presentation is as an abdominal lump or upper GI bleeding[3]. On rare occasions, however they can also manifest as a part of a tumor syndrome, such as CARNEY'S triad (gastric GIST, paraganglioma and pulmonary chondroma).

Based on their phenotypic features, they can be roughly divided into three major categories

Tumors showing differentiation towards smooth muscle cells which usually express Smooth Muscle Actin (SMA), desmin, calponin, myosin etc.

Tumors showing differentiation towards neural elements which show neural like features such as long cytoplasmic processes, dense core neurosecretory granules etc. These tumors have been called as Gastrointestinal Autonomic Nerve Tumours (GANTS) or Plexysarcomas. They have a greater malignant potential as compared to GISTs and these tumors exhibit non specificity in immunohistochemical markers like NSE and S-100.

Tumors showing dual differentiation both towards smooth muscle and neural elements.

Macroscopic findings

They may be single or multiple and vary in size from tiny intramural lesions to bulky tumor masses. Most neoplasms protrude from the outer surface as exophytic subserosal lesions. They are usually well circumscribed, nodular or bosselated masses and lack a true capsule. The cut surface is gray to pink in color with a rubbery consistency. It lacks the whirling smooth muscle pattern of leiomyomas.

Microscopy

The two basic histopathological types of GIST are the spindle and epithelioid varieties.

Spindle cell GIST

They are composed of interlacing bundles or whorls of uniform spindle shaped cells with ovoid nuclei and fibrillary eosinophilic cytoplasm which may contain a clear paranuclear vacuolae. Skeinoid fibres, which are small, globular or curvilinear eosinophilic aggregates of filamentous material may be scattered among the tumor cell

Epitheloid GIST

They occur more commonly in antrum and consist of round vacuolated or clear cells arranged in cohesive sheets or nests which impart an epithelioid pattern. Nuclei are round to ovoid, with finely dispersed chromatin and small nucleoli.

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Immuno-histochemistry

Most important advance in the diagnosis of GIST is the discovery of CD-117(c-KIT), a tyrosine kinase receptor expressed by the interstitial cells of Cajal. More than 95 % of the tumors are positive for CD – 117 and the diagnosis of GIST should be questioned when the tumor is CD- 117 negative [4]. Staining is usually strong and widespread and may be distributed in the cytoplasm, localized to a perinuclear dot, or membranous. Since CD 117 is a tyrosine kinase receptor, it explains the fact that some of these tumors are sensitive to the action of Imatinib mesylate (a tyrosine kinase inhibitor).

A small number of GISTs may have mutations in another gene called as the platelet derived growth factor receptor alpha (PDGFRA). Most gastric GISTs also express CD-34. Few might show positivity with smooth muscle actin, desmin or S–100.

	SIZE(cm)	MITOTIC COUNT(PER 50 HPF)
Very Low Risk	<2	<5
Low Risk	2-5	=5
Intermediate Risk	=5 5-10	6-10 =5
High Risk	>5 >10 Any size	>5 Any mitotic rate >10

Predicting behavior

The behavior of GISTs can be predicted by the estimation of the size of tumor and the mitotic rate[5]. The various guidelines given by Fletcher CDM are:

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Figure 1: High power view of a gastric GIST showing spindle shaped cells arranged in a pallisading pattern

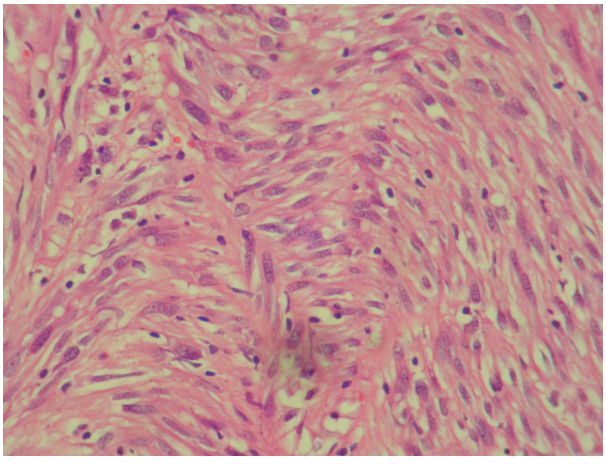
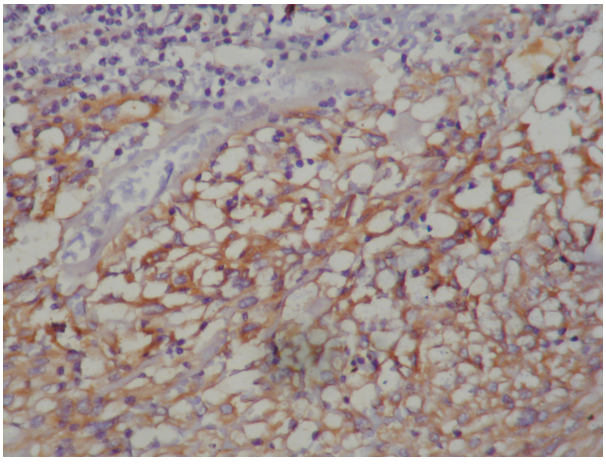


Figure 2: Photomicrograph showing CD-117 positivity



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Tissue engineering

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Tissue engineering applies the principles of engineering and life sciences towards the development of biologic substitutes that restore maintain or improve tissue function[1]. The aim of tissue engineering is to develop alternative methods of tissue replacement that eliminate the complications caused by damage to normal tissue traditionally harvested as graft or flaps. Tissue engineering has been made possible by the fusion of clinical surgery, engineering and biology.

The earliest examples of tissue engineering relate to the introduction of biomaterials such as silicone gel breast implants which have been clinically used since 1960s[2]. The second phase started in 1970s and saw the designing of glass and calcium ceramics for bone replacement. A number of biodegradable synthetic polymers that are used as absorbable suture materials came in to clinical usage and are another example of tissue engineering. Presently we have biodegradable materials that could serve as a temporary scaffold for cell attachment and guide tissue formation undergoing clinical trials[3].

In the domain of plastic surgery, tissue engineering represents a fundamental advance because it modifies tissues at the level of cells and molecules, thus allowing surgeons to alter tissues in a manner that is as sophisticated as their ability to transfer tissues. The clinical goals are timely healing, maximal functional and aesthetic restoration and minimal morbidity. Moreover tissue engineering allows tissue replacement to be as patient specific as possible.

Engineering tissues for anatomic defects in cancer patients pose special problems. The excision defects in such patients consist of a combination of several tissue types, each of which must be taken into consideration at the time of reconstruction. Adjuvant radiotherapy makes the local tissue unreliable and the risk of local recurrence should be kept in mind at the time of planning reconstruction.

The principles of tissue engineering can be well illustrated in the designing of a replacement for a segmental mandibular defect. The fundamental steps would consist of

1. Identification of missing tissue elements and precise dimensions of the defect
2. Fabrication of a computer assisted custom device of scaffolding material as per specifications of defect
3. The device would consist of a hollow chamber containing bioactive factors and a porous degradable tissue conducting scaffold.
4. Implantation of the device into the defect to guide three dimensional tissue and blood vessel in growth.
5. The bioactive factors within the device would consist of cells with osteogenic potential harvested from the patient along with recombinant growth factors.

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6. An alternative method could be to place the scaffold device at a distant site such as the inner table of ileum and allow the patient to grow a replacement part into the degradable scaffold prior to its implant into the mandible[4].

Making this mandibular substitution a possibility would require inputs form computer software specialists, biomaterial development and biotechnology.

Biomaterials

Several varieties of biomaterials are used in tissue engineering as implantable devices such as tissue molding chambers, tissue scaffolds and bioactive material delivery vehicles. Molds are used to guide tissue formation into predetermined shapes and help direct blood supply to facilitate surgical transfer. Titanium, silicone, rubber and polymethacrylate have been clinically used as tissue molds[5].

Another usage of biomaterials is as tissue scaffolds. For this purpose the material should be biocompatible, degradable and should have good tissue conductivity. Compounds used for this purpose are hyaluronin, glycosaminoglycans, collagen and fibrin. Synthetic polymers provide greater design flexibility. Degradable polymers have chemical bonds that undergo hydrolysis on exposure to aqueous body fluids, or undergo cellular digestion or enzymatic degradation. The rate of degradation is influenced by porosity, hydrophobicity, copolymer ratio and crystallinity. The commonly used synthetic scaffolds are made of biodegradable polymers and calcium ceramics. Bioactive molecules can be incorporated into the scaffold or mold which is released as the material disintegrates.

Biotechnology

Biotechnology aims to understand, alter or direct the function of organic cells. These include techniques of cell transplantation as well as in vivo cell recruitment. Cell harvesting involves harvesting cells, expanding and if required modifying them in culture and then transplanting them back to the donor to restore tissue function. Stem cells because of their pluripotential nature and ability to divide in culture are especially useful for cell transplantation. The differentiation of stem cells can be directed in to particular specialized cells by modifying culture conditions. A number of growth factors and hormones can be used during the tissue culture process to co-ordinate specialized tissue formation and angiogenesis. Genetic engineering can be combined with cell culture technology to produce tissue replacements with improved function. Natural tissues can be altered to produce increased quantities of growth factors and will function as implantable living protein secretory devices.

Tissue substitution

Skin, adiopose tissue, musculoskeletal and vascular tissues have all been replaced. The most successful skin substitute is cultured human keratinocytes on an acellular dermis or fibroblast bed. This has been use din burns, diabetic and venous foot ulcers. For adiopose tissue replacement, autologous preadiopocyte culture techniques are being tried in mastectomy patients[6]. Cartilage repair by autologous cultured chondrocyte implantation is clinically available. Chondrocytes have a low metabolic rate and therefore function well under low oxygen tension. Articular cartilage has been designed from polyglycolic acid, calcium alginate and polypropylene. Secure healing of the engineered cartilage to the underlying bone is obtained by a composite of porous calcium ceramic on one surface to obtain osseous integration and a chondrocyte seeded scaffold towards the joint surface[7]. Investigators are focusing on tissue substitution techniques for bone and musculoskeletal elements like tendons, ligaments and skeletal muscle fabrication.

The biggest limiting factor in tissue engineering is the development of a viable capillary network capable of maintaining tissue viability. Delivery of angiogenic growth factors has had only a limited success. Approaches to develop lengths of vascular conduits from smooth muscle and endothelial cells cultured under pulsatile conditions have been tried[8]. These conduits had good handling

and functioning including contractile response to pharmacological agents and showed patency 24 days after implantation in animals.

Developments in tissue engineering will depend on cooperation among engineers, biologic scientists and clinicians. Although laboratory experiments have been successful, ultimate progress will depend on the ability to develop marketable products. Acceptable safety and efficiency standards for tissue engineering products also need to be defined. Embryonic stem cells which can terminally differentiate into all types of somatic cells are considered a promising source of seed cells for tissue engineering.

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Fibroadenoma in Unusual Site

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IN BRIEF

Fibroadenoma is one of the most common benign breast disease seen in women in their late teens. Although ectopic benign breast tumour is more common along "Hughes line", can also have an ectopic location., Whatever the position of ectopic breast tissue, it can undergo the same pathologic changes as seen in normally positioned breasts such as fibroadenoma and carcinoma., We report a case of fibroadenoma in unusual site, in 25year old female, who presented with painless swelling in the left infra-axillary region since 6months. It was diagnosed as fibroma or rare one fibroadenoma in axillary tail clinically., Fine needle aspiration cytology revealed benign fibro-epithelial lesion. The swelling was excised in toto and processed for histopathological examination. Histopathological examination confirmed fibroadenoma similar to the conventional type arising in the normal breast tissue.

Key words: Fibroadenoma, Unusual site

Introduction

Fibroadenoma is one of the most common benign breast disease seen in women in their late teens, accounting for 7-13% in breast clinics[1].The incidence of extra-mammary fibroadenomas is 1-6% in general population and is most commonly seen along the milk line[2]. The unusual locations are usually referred as "mammae erraticae" i.e. vulva, eyelid, face, peri-anal, buttock, pubic region[3].

Though polythelia is congenital in origin, the ectopic mammary tissue appears during puberty, pregnancy and puerperium due to sex hormones[4]. The cases of ectopic breasts with benign tumors, cystic changes and carcinomas have been documented[5].

We report a rare case of fibroadenoma in the axillary tail, which will be one of the differential diagnosis of axillary mass[6].

Case report

A 25year old female presented with a painless swelling in the left infra-axillary region since 6 months. The swelling increased in size over the last 2 months. There was no history of similar swellings anywhere over the body. No personal or family history of breast malignancy.

The clinical examination revealed a single, oval shaped swelling in the left infra-axillary region measuring 3x2x2cms. (fig1).

The swelling was firm, non-tender, freely mobile and completely isolated from the left axilla and left breast contour. Clinically both mammary glands and axillae appeared normal. Systemic examination revealed no abnormalities. Clinically it was diagnosed as a fibroma or a rare case of fibroadenoma in the axillary tail.

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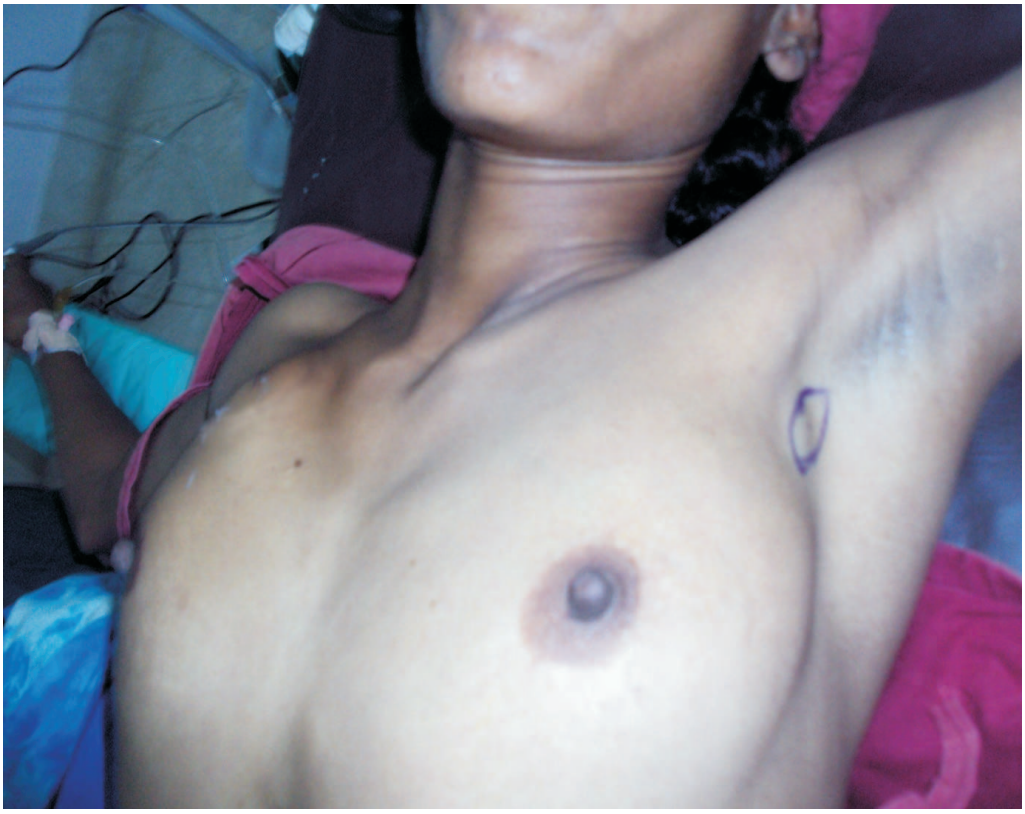
Fig1. A small swelling in the left infra-axillary region



FNAC of swelling revealed it to be a benign fibro-epithelial lesion with signs of hyperplasia(fig2). The swelling was subjected to histopathological examination after complete excision.

Gross examination

Single tissue piece of size 3x2x2cms soft to firm in consistency. Cut surface was greyish-white in colour(fig3).

Fig 2: FNAC revealed loose to cohesive aggregates, branching fragments and scattered plump ductal cells. Few show large nucleus and variable cytoplasm. Background has scattered round bare nuclei, leucocytes and RBCs.

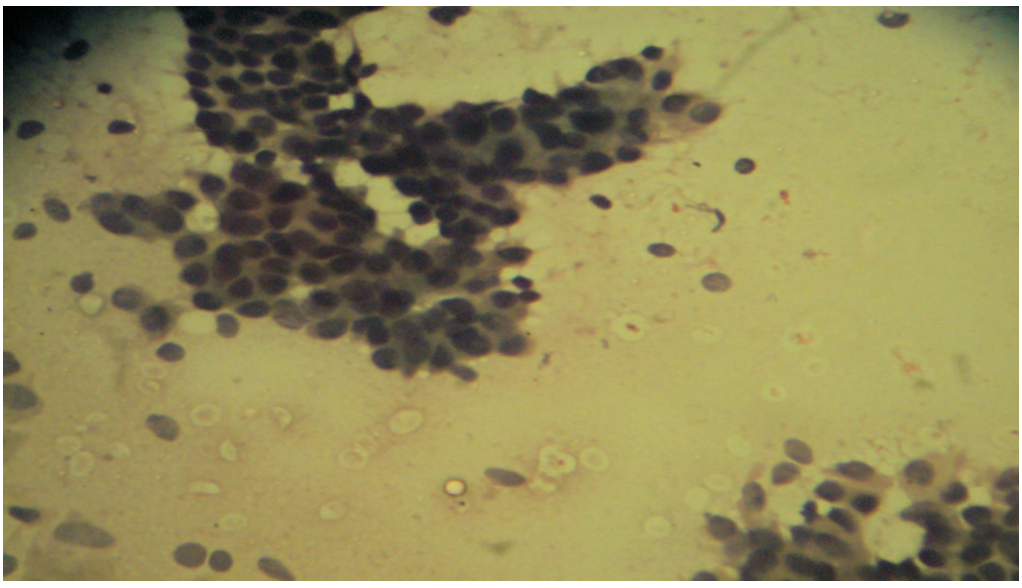


Fig 3: Surgically excised specimen.

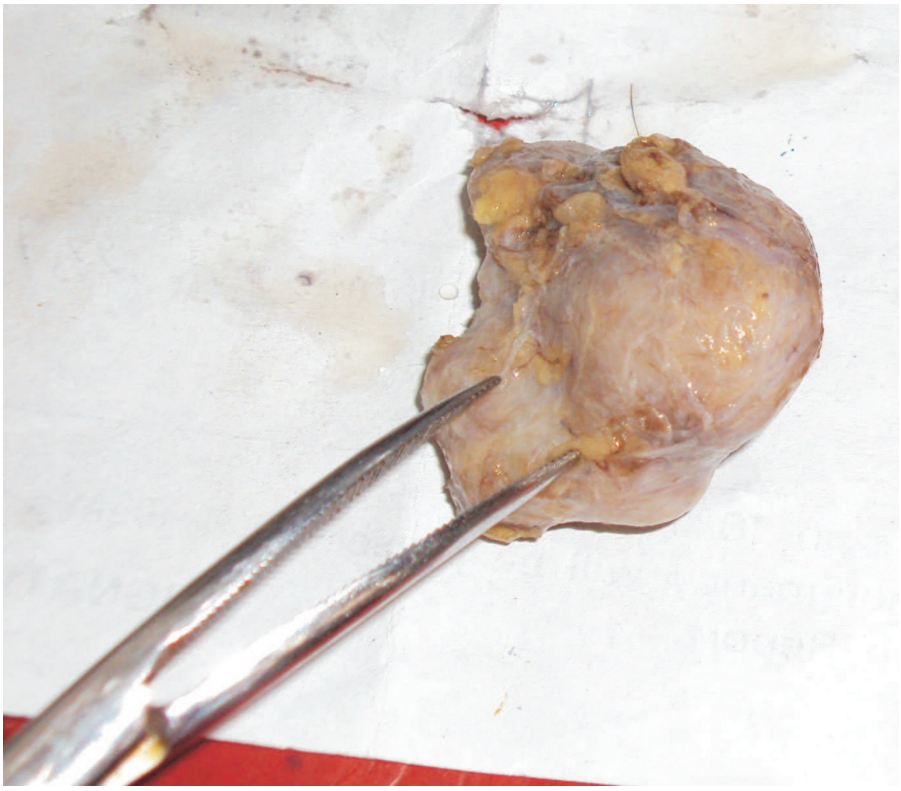


Fig 4: Post operative histopathologicalexamination showed a capsulated benign tumour composed of proliferation of ducts and stroma. Some of the ducts are circular and some are lined by bilayered benign epithelium. Stroma is myxoid

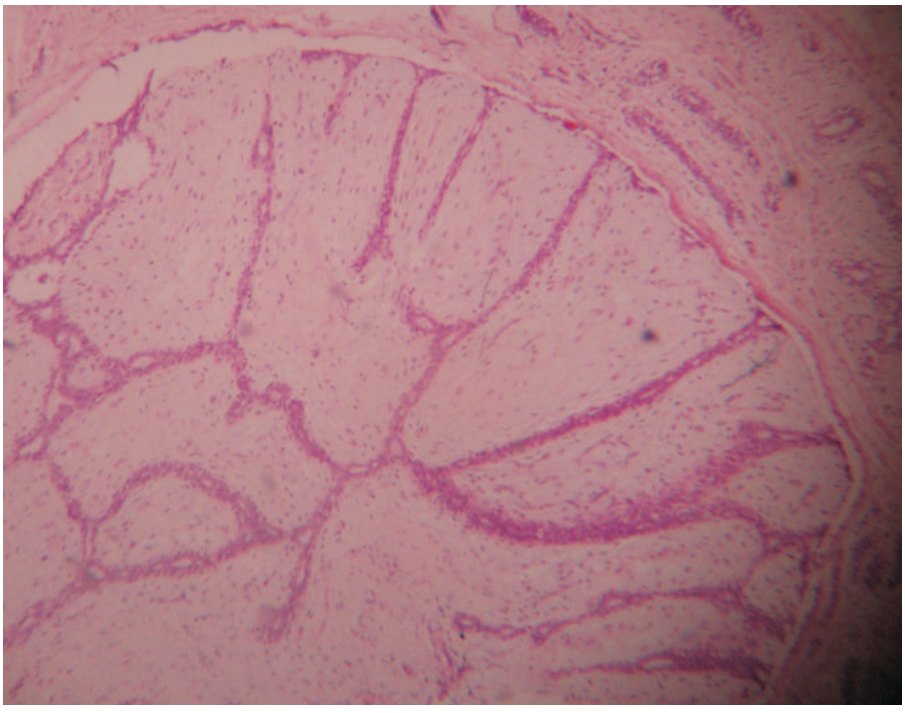
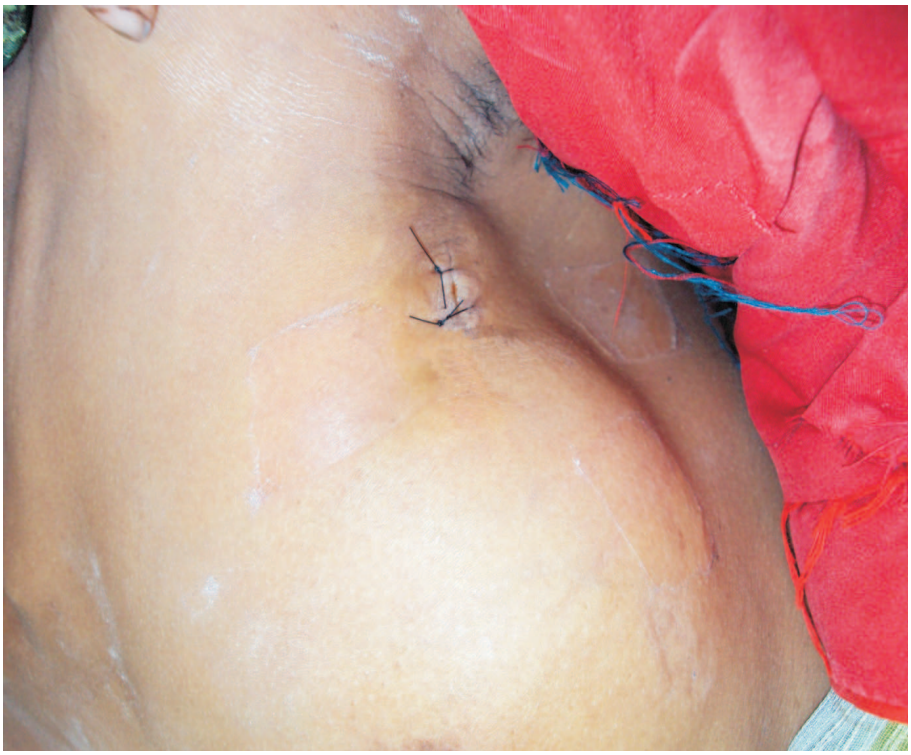


Fig 5: Operative scar following surgical excision of the swelling.



Microscopic examination

A benign tumour, composed of proliferation of ducts and stroma lined by bilayered benign epithelium, characteristic of intra-canalicular type of fibroadenoma(fig4).

The post operative scar seen in the left infra-axillary region(fig. 5).

Discussion

The fibroadenoma is one of the most common benign breast disease seen in women in their late teens accounting for 7-13% patients in the breast clinics[1]. The incidence of fibroadenomas at extra-mammary sites varies from 1-6%[2]. The milk line extends from the axilla to the groin or pubic region[3].

The most cases of supernumerary mammary tissue are described as masses localized within the milk line. The axilla is by far the most frequent location and seldom under valorised because it is mistaken for an enlarged lymph node[3-6,7]. Any mass localized along the mammary ridges should always raise the suspicion of mammary tissue.

Although rare, unusual locations of ectopic breast tissue have also been reported in the literature as "mammae erraticae", such as over the face, eyelid, back of neck, pubic region etc. The ectopic breast tissue has the same physiology and can be the origin of same pathology as normally positioned breasts. The literature mentions of ectopic breasts with benign cystic changes, benign tumours (adenoma and fibroadenoma) and carcinomas[5,7].

There are three types of fibroadenomas; soft, hard and giant (>5cms in size). The giant variety is common in Africa. Microscopically it can be intra-canalicular and pericanalicular[8].

Fortunately the ectopic tissue often represents only a cosmetic problem. In this view, it can be surgically excised and also whenever there are symptoms such as local discomfort or tenderness with milk secretion.

In cases of malignant mass, wide surgical excisions are recommended with appropriate follow up treatment[9].

Polythelia is associated with urinary tract abnormalities such as supernumerary kidneys, failure of renal formation and renal carcinoma, diagnosed by ultrasonography[10]. The presence of extra-nipple in children should always raise the clinical suspicion of renal and urinary tract abnormalities.

In our case, the patient did not have polythelia or polymastia. Anatomically both mammary glands were normal. There was no axillary mass present.

In conclusion, when a swelling is found in the mammary ridge, ectopic breast tissue and all the pathologic changes of breasts must be kept in mind, because early diagnosis leads to better prognosis in case of malignancy.

The ectopic breast malignancy can present a challenge for clinician and pathologist in making correct diagnosis.

In extra-mammary lesions, renal imaging should be considered after a confirmed histopathological diagnosis.

Further research is needed to more deeply understand this phenomenon and its associations and the appropriate clinical workup in such cases.

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Micropapillary Urothelial Carcinoma – A Rare Aggressive Variant

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Agrawal Usha***
Mohanty N.K.****

IN BRIEF

Urothelial neoplasms are a heterogeneous group of lesions, of which urothelial carcinoma is known for its divergent differentiation. Although majority of tumors are transitional cell carcinomas, the morphological spectrum of bladder cancer has expanded to include many new variants. The importance of recognition of these variants lies in the diagnostic, prognostic and therapeutic considerations that may occur as a result of a particular diagnosis. One such variant is micropapillary urothelial carcinoma [MPC]. Micropapillary carcinoma is an extremely rare but aggressive variant of urothelial carcinoma. The presence of this carcinoma should alert the urologists of its high grade and stage. We report a new case of bladder MPC in a 55year old male and highlight the significance of recognizing this aggressive tumor.

Keywords: Micropapillary, urothelial carcinoma

Introduction

Bladder cancer is reported to affect thousands of patients each year. Although the majority comprises of transitional cell carcinoma, recognition of micro-papillary [MPC] variant is important in view of its ramifications for prognosis as well as approach to therapy. MPC was first described as a distinct pathological entity by Amin in 1994[1]. The histological features were distinctly reminiscent of papillary configuration seen in ovarian papillary serous tumors.

Histopathologically, the papillary component appears as clusters of cells with peripherally arranged nuclei, creating a rosette-like pattern. Clear spaces are seen surrounding the cells. Nuclei may vary in degree of anaplasia but most are high grade. The molecular characteristics of these tumors are poorly understood, probably due to their rarity[2].

Case report

We report a case of a 55 year old gentleman who presented to the Urology OPD with complaints of painless hematuria off and on for the past one and a half years. Contrast Enhanced CT scan of the abdomen revealed a growth measuring 4.5 x 3 x 2 cms in the postero- lateral wall of the bladder along with enlarged intra-peritoneal lymph nodes.

Cystoscopic examination revealed a solid mass with some papillary projections present on the postero- lateral wall of the bladder. The patient underwent a transurethral resection of the bladder tumor (TURBT) and the tissue was sent for histopathological evaluation. On gross exmaination, multiple friable grey white pieces of soft tissues were seen. Microscopically, the neoplasm showed few short filiform papillae, some of them with fibro-vascular cores. The neoplastic cells showed moderate to marked pleomorphism

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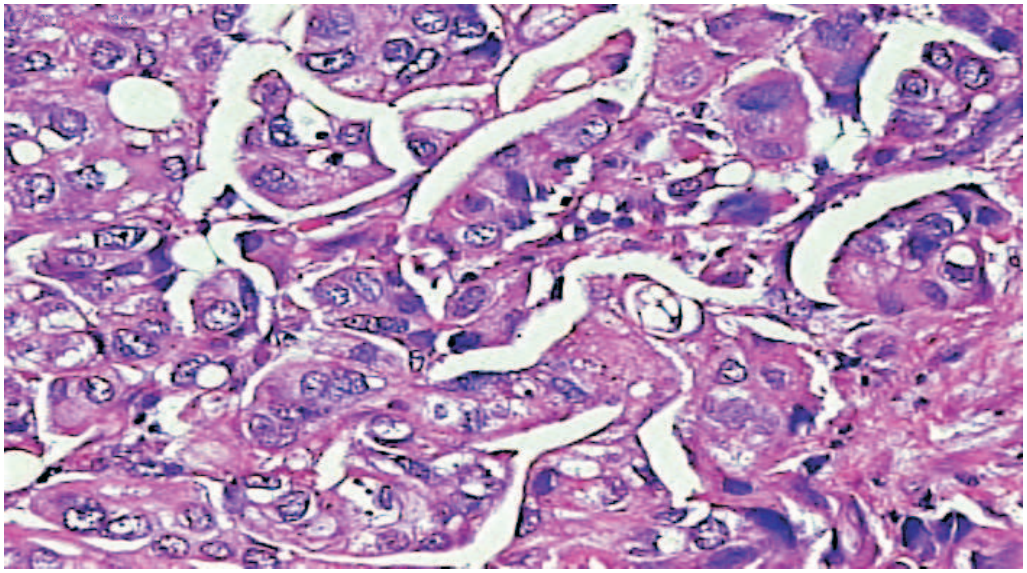
Figure 1: Photomicrograph (40 X H&E) showing tumor cells arranged in a micropapillary configuration. Marked pleomorphism is seen in the tumor cells and cells are seen to be arranged in clusters with a clear space around them



and were arranged in clusters surrounded by clear spaces lacking endothelial lining [Figure 1]. The bladder muscle was seen to be infiltrated by tumor cells. The mitotic count varied from 6 to 8 mitosis per 10 high power fields.

In view of the aggressive nature of the neoplasm, the patient underwent a radical cystectomy with formation of ileal conduit.

Discussion

Micropapillary urothelial carcinoma [MPC] of the urinary bladder is a rare tumor. The overall incidence of these tumors is unclear, and it has been suggested that the incidence may be greater than currently reported[3].

There is a clear male predominance with a male: female ratio of 5:1 to 10:1 and it usually presents in the fifth to ninth decade of life [4,5]. After the initial recognition of MPC in the urinary bladder, additional reports of this entity within the ureter and renal pelvis have been reported in more recent years[6,7].

Histopathologically, the micropapillary variant is characterized by a surface component of slender delicate filiform papillary projections with secondary or tertiary branching without fibrovascular cores[4,8]. Samaratunga et al. in their study, however noted that some papillae contained central fibrovascular cores while others were devoid of them[9]. The invasive component consists of tightly cohesive nests lying in small clear spaces which lack endothelial lining[4,5,8,9]. This pattern is especially characteristic of MPC and is retained at metastatic sites. Awareness that these lacunae may mimic vascular-lymphatic invasion is important to prevent over diagnosis as it is an adverse prognosticator in urothelial carcinoma[4]. The present case also showed these histopathological findings. The mitotic count in MPC varies from few mitosis to numerous mitosis per high power field. Samaratunga et al. reported it to vary between 3 and 34 per 10 high power fields[9]. In our case the mitotic count varied from 6 to 8 per 10 high power fields. MPC is such an aggressive tumor, that even in the absence of muscularis propria in the biopsy, muscle invasion is assumed and thus, these patients should be managed aggressively[2,8].

Diagnosis of this variant is not difficult because of its unique morphology hence immunohistochemistry [IHC] for diagnosis is not necessary[5]. Distinction from other entities has not been a problem for those aware of this variant[2]. Metastatic MPC of the bladder can mimic metastatic carcinoma from ovary, breast and lung which are morphologically similar

to MPC. It is important to be able to distinguish between these tumors as treatment and prognosis are different for each. This differentiation can be made on the basis of IHC. MPC of urothelial origin is positive for CK7 and CK20 while those of ovarian, breast or lung origin are most likely CK7 positive but CK20 negative[4,5,8,9]. CA-125 immunoreactivity is seen in 35-43% cases of MPC of urothelial origin[9].

There is no standard treatment protocol for the management of MPC[8]. The role of chemotherapy in the treatment of patients with micropapillary bladder cancer remains to be elucidated. Some studies have suggested that neo-adjuvant chemotherapy is ineffective in micropapillary variant of bladder cancer[8,10]. Intravesical Bacillus Calmette Guerin (BCG) therapy is also often ineffective in cases of MPC[4]. In light of minimal success with chemotherapy or radiotherapy, radical cystectomy is indicated. A study by Kamat et al. suggested that, once a diagnosis of micropapillary bladder cancer has been made, every attempt should be made to facilitate an expeditious radical cystectomy[10].

The importance in identifying this unusual histological variant resides in its dismal prognosis. It has a tendency to present at high stage. Patients typically present with usually an advanced stage of disease [III or IV] at the time of diagnosis[8].

In conclusion, micropapillary type of urothelial carcinoma is a rare variant of bladder cancer with high metastatic potential and poor prognosis. Radical cystectomy provides a chance of cure in patients with surgically resectable disease. Therefore, recognition of this subtype is extremely important. The poor outcome of the patients emphasizes the need for an early and accurate diagnosis and treatment.

Conflict of interest- None

The manuscript has been read and approved by all the authors, and the requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work.

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Fishbone perforation of Meckel's diverticulum: An unusual case of right iliac fossa pain

Ravikant Narain

IN BRIEF

Perforation of a Meckel's diverticulum by a foreign body is a rare occurrence and can mimic. A 45 year old gentleman presented with signs and symptoms suggestive of acute appendicitis and a decision was taken to operate the patient. On exploration, the appendix was found to be normal and a fish bone was seen to be protruding through the Meckel's diverticulum. The diverticulum was resected and end to end anastomosis was done. Patient had an uneventful recovery

Case Report

A 45 year old soldier was air evacuated with complaints of acute onset pain abdomen for the last one day. Patient developed sudden onset peri-umblical pain followed by two episodes of bilious vomiting. The pain over a period of one day got localized to the right iliac fossa.

On clinical evaluation, the patient's vitals were stable except for mild tachycardia and low grade fever. Abdomen was not distended and rebound tenderness was present in the region of the right iliac fossa. His hematological and biochemical parameters were essentially normal. A clinical diagnosis of acute appendicitis was made and patient was taken up for emergency appendectomy.

Grid iron incision was made and the peritoneum was incised. On exploration, however, the appendix was essentially normal. On searching the terminal ileum, a Meckel's diverticulum was delivered. Protruding out from the diverticulum was a fish bone of size 3.5 cms. The fish bone had successfully traveled down till the diverticulum and got stuck in the abnormal anatomy. The sharp end of the bone perforated the diverticulum and caused local peritoneal signs of peritonism, mimicking appendicitis. The diverticulum along with the normal gut was excised and a hand sewn double layered side to side ileo-ileal anastomosis was done through the same incision. The patient recovered satisfactorily and discharged on the tenth day.

Discussion

Meckel's diverticulum is found in 2 or 3 per cent of all cases coming to autopsy. It is said to be more common in males than in females, the ratio being about 3:1. Around 100 cases of foreign body perforation of Meckel's diverticulum have been reported in the literature. The youngest case was reported in an 18 month old child whereas the oldest case was reported in a 75 year old gentleman[1-8].

In the majority of perforations, history of an ingested foreign body was lacking and operation usually was done on the basis of a diagnosis of appendicitis. In those cases where foreign body ingestion was known it was correctly implicated as the cause of symptoms prior to operation[1-3]. Fish bone was the commonest cause of Meckel's diverticulum perforation[2,7].

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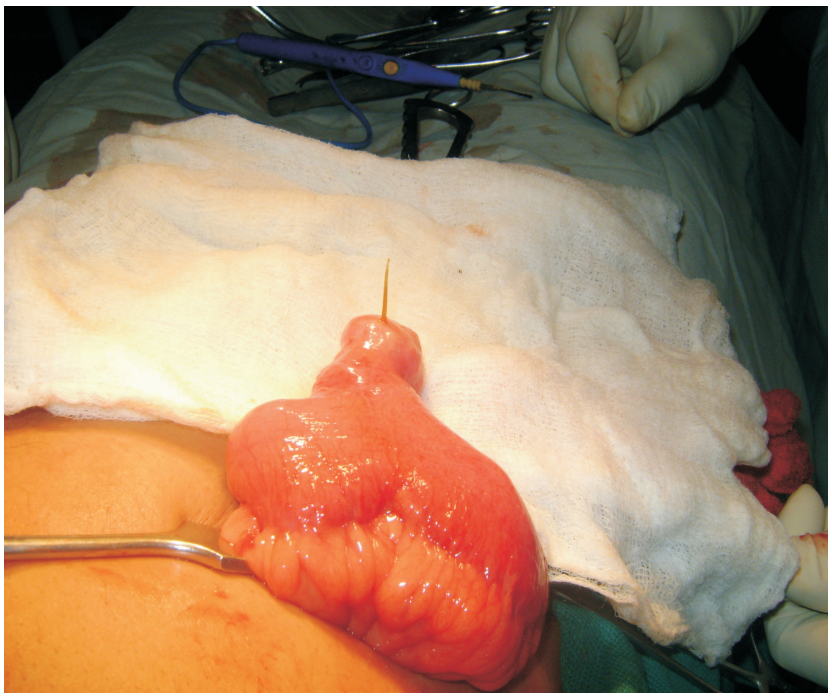
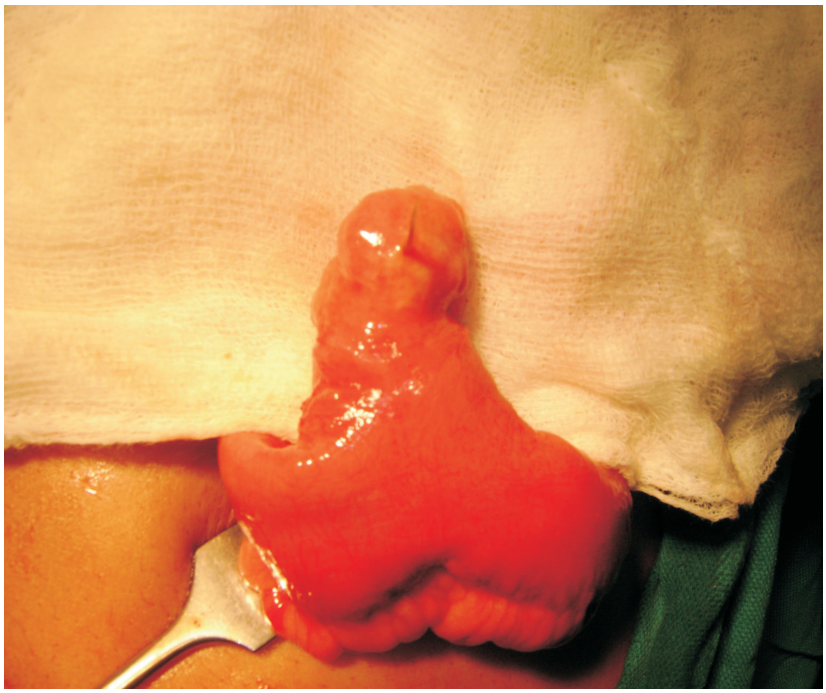
Figure 1: Fishbone protruding through the Meckel's diverticulum





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Benjamin Lewin. Genes VI. New York; Oxford University Press, 1997

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Fisher M. Nosocomial. Infection and Infection Control. In Jenson H, Baltimore R. Pediatric Infectious Diseases. 2nd Ed, W.B. Sounders Company; 2002: 1221.

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Jutta M. Joesch et al. Does Your Child Have Asthma? Filled Prescriptions and Household Report of Child Asthma. Elsevier. http://www.jpedhc.org/article/S0891-5245(06)00129-5/abstract (August 21, 2008).

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Postgraduate surgical master quiz

1. Level-II lymph node corresponds to which anatomical lymph node group in the neck

a. Upper deep cervical
b. Middle deep cervical
c. Submandibular group
d. Submental group

2. Minimum biopsy for a thyroid malignancy is

a. Trucut biopsy
b. Fine needle aspiration cytology
c. Hemithyroidectomy
d. Incisional biopsy

3. Psammoma bodies are observed in

a. Papillary carcinoma thyroid
b. Hodgkin's disease
c. Follicular neoplasm of thyroid
d. Infectious mononucleosis

4. The only vital anatomical structure traversing lateral to medial in the neck is

a. Vagus nerve
b. Phrenic nerve
c. Bracheal pleaxus
d. Sympathetic chain

5. Modified neck dissection Type-I involves preservation of

a. Vagus nerve
b. Spinal accessory nerve
c. Internal jugular vein
d. Sternocleidomastoid muscle

6. Scrofula is observed following which infection

a. Tuberculosis
b. Staphylococcus aureus
c. Streptococcal infection
d. None of the above

7. The deltopectoral flap is based on

a. Thoraco-acromial artery perforators
b. Internal mammary artery perforators
c. Subclavian artery
d.Pectoral branch of thoracoacromial artery

Answers of this quiz with explanation will be given in the next issue of this journal

Journal Scan

Ann Oncol. 2010 Nov 25

Expression of androgen receptor in breast cancer and its significance as a prognostic factor

Yu Q, Niu Y, Liu N, Zhang JZ, Liu TJ, Zhang RJ, Wang SL, Ding XM, Xiao XQ.

Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital.

Abstract

Background: Breast cancer is an extraordinarily hormone-dependent tumor. This study was to evaluate androgen receptor (AR) status and its significance in breast cancer in Chinese women.

Method: Three hundred and thirty-five consecutive cases of invasive ductal breast carcinoma, 34 ductal carcinoma in situ (DCIS), and 82 DCIS adjacent to invasive tissues were involved in this study. The expression of AR was analyzed by immunohistochemistry and compared with patient outcome, and its implications were evaluated in five molecular subgroups of invasive ductal carcinoma (IDC) and in DCIS lesions.

Rresults: AR expression was related to that of estrogen receptor ($P < 0.001$) and progesterone receptor ($P = 0.035$) but not correlated with the other conventional parameters. AR retained independent prognostic significance (hazard ratio 0.309, 95% confidence interval, 0.192-0.496; $P < 0.001$). The majority (61.0%) of basal-like breast cancers showed loss of AR expression ($P < 0.001$), which had poor prognosis. The percentage of AR-positive cases was significantly higher in DCIS adjacent to IDC group than in pure DCIS and IDC groups (93.9%, 79.4%, and 72.5%; $P = 0.046$ and $P < 0.001$, respectively).

Conclusion: Our data suggest that AR may provide another specific definition of breast cancer subtypes and reveal a potential role in DCIS progression. These findings may help develop new therapies.

Am Surg 2010 Oct; 76(10): 1119-22

Time from diagnosis to surgical treatment of breast cancer: factors influencing delays in initiating treatment

Wright GP, Wong JH, Morgan JW, Roy-Chowdhury S, Kazanjian K, Lum SS.

Department of Surgery, Division of Surgical Oncology, Loma Linda University School of Medicine, Loma Linda, California 92350, USA.

Abstract

No clear guidelines exist defining the appropriate time frame from diagnosis to definitive surgical treatment of breast cancer. Studies have suggested that treatment delays greater than 90 days may be associated with stage migration. We sought to evaluate demographic factors that influence 30-day and 90-day benchmarks for time from diagnosis to definitive surgical treatment of breast cancer. Between 2004 and 2007, 19,896 women with stage I to III invasive breast cancer were treated with primary surgical therapy and did not receive preoperative systemic therapy in the California Cancer Registry. Overall, 75.7 per cent of patients were treated within 30 days of diagnosis, and 95.5 per cent of patients were treated within 90 days of diagnosis. Multivariate analyses revealed that treatment delays were associated with smaller tumor size, use of total mastectomy, lower socioeconomic status, and Hispanic and non-Hispanic black race/ethnicity. Furthermore, disparities in those that did not meet 30-day benchmark timeframes were exaggerated with 90-day treatment delays. These benchmarks can be used to measure disparities in health care delivery.

Am Surg 2010 Oct; 76(10): 1127-9

Axillary recurrence after sentinel lymph node biopsy for breast cancer

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Abstract

Sentinel lymph node biopsy (SLNB) is routinely performed as an axillary staging procedure for breast cancer. Although the reported false-negative rate approaches 10 per cent, this does not always lead to axillary recurrence. We previously reported an axillary recurrence rate of 1 per cent at a median follow-up of 2 years. Our objective is to determine the rate of axillary recurrence with longer follow-up. A retrospective review of patients with invasive breast cancer and a negative SLNB treated between 2001 and 2005 was performed. Cases where neoadjuvant therapy was used or where isolated tumor cells (ITCs) were found were included, whereas those with fewer than 18 months of follow-up were excluded. One (0.7%) out of 139 patients had an axillary recurrence after a median follow-up of 52 months. No patient who underwent neoadjuvant chemotherapy or with ITCs had axillary recurrence. Twelve (8.6%) patients have died, with death attributed to breast cancer in three. Our study demonstrates that axillary recurrence after SLNB remains a rare event after a median follow-up of 52 months, despite including potentially higher risk scenarios such as where neoadjuvant chemotherapy is used and ITCs are found. Therefore, axillary lymph node dissection can safely be avoided in patients where SLNB is negative.

Ann Surg Oncol. 2010 Nov 24

Is pT2 Subclassification Feasible to Predict Patient Outcome in Colorectal Cancer?

Tong LL, Gao P, Wang ZN, Yue ZY, Song YX, Sun Z, Lu Y, Xing CZ, Xu HM.

Department of Surgical Oncology and General Surgery, The First Hospital of China Medical University, Shenyang, People's Republic of China.

Abstract

Background: This study aimed to evaluate the prognostic impact of pT2 sub-classification according to the depth of muscularis propria (MP) invasion and to explore the clinic-pathologic factors correlated with lymph node metastasis (LNM) and postoperative hematogenous metastasis in pT2 colorectal cancer.

Methods: A total of 317 patients with pT2 colorectal cancer were reviewed. pT2a represents the infiltration of the inner circumferential layer of the MP, and pT2b represents the infiltration of the outer longitudinal layer of the MP. Clinicopathologic factors and overall survival rates were compared in patients with pT2a and pT2b stage cancers. Multivariate analysis was performed to identify the significantly important prognostic factors. Univariate and multivariate analyses were performed, respectively, to identify the significantly important clinicopathologic factors correlated with LNM and postoperative hematogenous metastasis in pT2 colorectal cancer.

Results: According to the depth of MP invasion, 107 patients were classified as pT2a and 210 patients were classified as pT2b. Among them, there were 55 patients with LNM, 34 patients with postoperative hematogenous metastasis. There was significant difference in most of clinicopathologic features between patients in the pT2a and pT2b stages. Multivariate analysis identified pN stage ($P < .001$) and tumor location ($P = .036$) were independent factors affecting the prognosis. However, no apparent difference was observed between pT2a versus pT2b cancer. Univariate and multivariate analyses uniformly identified lymphovascular invasion ($P = .035$) and the depth of MP invasion ($P = .005$) as significantly correlated with LNM. Multivariate analysis found tumor location ($P = .021$) and the presence or absence of LNM ($P < .001$) were important factors affecting postoperative hematogenous metastasis.

Conclusion: In pT2 colorectal cancer treated with R0 surgery, there is a high risk of LNM in deep MP invasion versus superficial MP

invasion. The pT2 subclassification system had no significant advantage in identifying a different prognosis, except for predicting the LNM before surgery. Rectal cancer and the presence of LNM were high-risk factors resulting in hematogenous metastasis postoperatively.

Am Surg 2010 Oct; 76(10): 1100-3

Surveillance with serial serum carcinoembryonic levels detect colorectal cancer recurrences in patients who are initial nonsecretors

Holt A, Nelson RA, Lai L.

City of Hope Comprehensive Cancer Center, Duarte, California 91010, USA.

Abstract

Serum carcinoembryonic antigen (CEA) levels, elevated in a subgroup of patients with colorectal cancer (CRC) at presentation, are serially followed as part of recommended surveillance after initial resection. The value of following serial CEA levels in patients who initially present with less than or normal levels of CEA (nonsecretors) is controversial. This study sought to determine the use of follow-up CEA levels in nonsecretors. A retrospective review was performed of patients with resected Stage I, II, and III CRC. We excluded patients who did not have a pretreatment CEA level, at least two follow-up CEA levels, or in whom CEA levels did not normalize after resection. The patients were grouped by initial CEA values: CEA 5 ng/mL or less (nonsecretors) and CEA 5 + ng/mL: (secretors). We identified 186 patients with CRC; 146 were initial nonsecretors. We identified 22 patients with recurrent colorectal cancer; 6 were secretors and 16 patients were nonsecretors. In the secretors group, CEA was elevated with recurrence in four (66%) of the patients. In the nonsecretors, CEA was elevated with recurrence in eight (50%) of the patients. In summary, many recurrences of CRC are marked by an elevation of CEA regardless of whether the patients initially presented as secretors or nonsecretors.

Tongue and Buccal Mucosa Carcinoma: Is There a Difference in Outcome?

Chun-Ta Liao MD, Shiang-Fu Huang MD, I-How Chen MD, Chung-Jan Kang, Chien-Yu Lin MD, Kang-Hsing Fan MD, Hung-Ming Wang MD, Shu-Hang Ng MD, Chuen Hsueh MD, Li-Yu Lee MD, Chih-Hung Lin, Tzu-Chen Yen MD, PhD

Head and Neck Oncology Volume 17, Issue 11 / November , 2010.

Background: We sought to determine the differences in clinical outcome of tongue and buccal carcinomas.

Methods: Five-year locoregional control, distant metastasis, and survival rates were examined in 456 patients with tongue cancer and 407 patients with buccal cancer.

Results: Five-year rates for patients with tongue and buccal carcinomas were as follows: local control, 85% and 87% (P = 0.9366); neck control, 81% and 87% (P = 0.0304); distant metastasis, 8% and 14% (P = 0.0052); disease-free survival, 70% and 72% (P = 0.9978); disease-specific survival, 79% and 78% (P = 0.2435), respectively. After stratification according to pathological lymph node status, patients with buccal cancer and pN0/pNx disease (without neck dissection) had a higher 5-year neck control rate than those with tongue cancer (93% versus 86%, P = 0.0115). In contrast, buccal cancer with pN+ disease had a higher 5-year distant metastasis rate compared with tongue cancer (30% versus 18%, P = 0.0231). In pN0/pNx subjects, neck control was predicted by perineural invasion and the absence of neck dissection in tongue cancer, and by poor differentiation in buccal cancer. In pN+ patients, distant metastases were predicted by pT3–4 disease, age at onset d”40 years, poor differentiation, and pN+ e” 5 nodes in tongue cancer, and by poor differentiation and pN+ e” 5 nodes in buccal cancer.

Conclusions: There are significant differences in the failure pattern of tongue and buccal carcinomas. Prognostic models for these malignancies should allow stratification of patients for a risk-adapted approach to treatment.