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Editorial

It is usual practice that the Editor writes a few words in every issue of the Malta Medical Journal. However, this time I am writing this brief introduction as the Chairman of the new editorial board of this Journal.

I would like to take this opportunity to thank the previous editorial board for the sterling work they have performed during their tenure of office. They have all worked incessantly in order to keep our Journal alive and for this, I believe, they merit our thanks.

A new Malta Medical Journal Editorial Board has now been appointed in order to continue this work. Professor Victor Grech has been appointed Editor, while Dr Christopher Barbara will take over the functions of Hon Treasurer. Professor Stephen Montefort, Professor Nikolai Attard, Mr Benedict Axisa, Dr Neville Calleja, Professor Stephen Fava, Dr Anthony Fenech, Mr Joseph Galea and Dr Alexander Gatt form the rest of the Editorial Board. Publishing and printing the Journal has always been a major problem and this will be one of the main priorities of this board. We shall try to overcome this problem by possibly making the journal readily available online. The Editorial Board will also strive to ensure a wider circulation for our Journal.

This is no easy task as it involves quite a laborious process but I am sure we will succeed as I am fortunate enough to have the collaboration of such a valid group of people on the Editorial Board. I am sure that with everyone's cooperation we will achieve our ultimate goal, that of continuing to improve the quality of our Journal.

Towards this end, your contribution is essential, as you, after all, are the contributors to our Journal and it is your important research and work that keeps the Journal alive.

Let us all continue with the excellent work done so far. We require your help, by submitting your work to be considered for publication in the Malta Medical Journal, in order to continue to disseminate valuable medical information to our medical community.

Raymond Galea
Chairman
Malta Medical Journal Editorial Board

Concordance with the British Society of Rheumatology (BSR) 2010 recommendations on eligibility criteria for the first biologic agent

Michela Frendo, John Paul Caruana Galizia, Andrew A Borg

Abstract

Aims: The aim of this study is to assess concordance with the British Society of Rheumatology (BSR) 2010 recommendations on the use of biologic therapy in Rheumatoid Arthritis (RA). The Disease Activity Score in 28 joints (DAS 28), a composite numerical score is included in these recommendations to assess disease activity and response to treatment.

Methods: Clinical notes of fifty patients who were commenced on biologic treatment between March 2010 and June 2011 were reviewed for documentation of DAS 28 scores at baseline, after approximately 6 months of commencement of treatment and at approximately 6 monthly intervals during treatment.

Results: Twenty two patients were eligible for this audit. Of these patients only half had a DAS 28 score performed prior to starting treatment, four patients had the score performed within 3-9 months of commencement of therapy and only 2 patients had continuous scores performed at six monthly intervals during treatment.

Conclusions: This audit shows that we are not adhering to the BSR recommendations. In order to improve our adherence we plan to train all staff in contact with patients on biologic treatment to perform DAS 28 scores and have a DAS 28 calculator readily available at out patients. A proforma is being developed for patients on biologic therapy to ensure that DAS 28 scores are performed at baseline and during treatment.

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Key Words
British Society of Rheumatology (BSR),
Disease Activity Score in twenty eight joints (DAS 28),
Disease Modifying Anti-Rheumatic Drugs (DMARDS),
Rheumatoid Arthritis (RA)

Introduction

Rheumatoid arthritis (RA), a systemic disease, is characterized by a chronic inflammatory reaction in the synovium of joints and is associated with degeneration of cartilage and erosion of juxta-articular bone. Many pro-inflammatory cytokines including tumour necrosis factor-alpha, chemokines, and growth factors are expressed in diseased joints.[1] Extra-articular features and systemic symptoms can also commonly occur.

RA has a worldwide distribution and an estimated prevalence of 1-2%. For many years non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate, sulphasalazine, leflunomide and hydroxychloroquine have been used singly or in combination to manage the disease. DMARD treatment has undergone dramatic changes over the past decade and biologic DMARD therapy has revolutionized the management of the disease.[2] The development of biologic DMARDS followed an increased understanding in the pathogenesis of inflammatory arthritis with the identification of cytokines which are key players in the inflammatory process. Their target is highly specific with the mode of action easier to elucidate than with traditional DMARDs.

Biologic drugs have allowed rheumatologists to satisfactorily control RA resistant to conventional DMARDs. All the biologic DMARDs are very expensive and their unrestricted use would be unaffordable.[3] Thus judicious use and review of such treatment is imperative to identify partial or non responders.

The BSR working party on biologic therapies started to work on guidelines to produce recommendations on the appropriate use of these therapies in RA in 2007. The three recommendations which were finalized and published in March 2010 are used in this audit.[4] They include eligibility criteria for biologic treatment and continuous monitoring of response to treatment using a validated score, the Disease Activity Score of 28 joints (DAS 28).

DAS 28 is a composite, numerical score combining several discrete measures of RA activity into a single grading of disease severity. It comprises objective (ESR), subjective (patient well being) and semi-objective (joint swelling and joint tenderness) criteria in 28 joints (including shoulder, elbow, wrist, metacarpophalangeal and proximal interphalagneal and knees) commonly involved in RA (Table 1).

Table 1: *How to calculate DAS28*

Variables	Result
Number of swollen (0-28)	
Number of tender joints (0-28)	
ESR (or CRP)	
Visual analogue scale (VAS) disease activity (0-100mm)	

How to calculate the DAS 28 score

1. Collect the data for the number of swollen and the number of tender joints, the ESR (or CRP) and the VAS for disease activity.
2. Use the equation below
   DAS28=0.56*√(TENDER JOINTS)+0.28*√(SWOLLEN JOINTS)+0.70*LN(ESR/CRP)+0.014*VAS

It is used to assess disease activity and monitor response to treatment with DMARDs. The European League Against Rheumatism (EULAR), published response criteria suggesting that biologics should be stopped if there is less than 20% improvement in DAS 28 at 3-6 months.[5] These response criteria were utilized by the BSR in the recommendations.

The above guidelines were chosen because they are recent, evidence based and comprehensive. If we are not adhering to the above recommendations we propose to implement change in our department to be consistent and give to our patients evidence based care.

The primary aim of this audit was to assess concordance of departmental management with BSR 2010 recommendations on biologic therapy use in RA. Secondary aims were auditing of the use of the DAS 28 prior to starting biologic therapy and its use to measure the response to treatment with biologic agents.

Patients and Methods

Patients

The demographic data of all patients with RA commenced on an anti-TNF agent and recorded in the database of the pharmacy department at Mater Dei Hospital from March 2010 to June 2011 were collected. The records held by the specialist nurse on patients receiving biologic therapy were also reviewed to ascertain completeness of recruitment of all the patients.

Methods

This is a retrospective audit. The case notes of the patients were reviewed to extract the following information:

1. DAS 28 score recorded at baseline (before starting treatment with anti TNF therapy).
2. Whether the DAS 28 score at baseline was appropriate for commencement of biologic therapy (i.e. ≥3.2).
3. Use of non biologic DMARD prior to starting anti –TNF.
4. DAS 28 scores recorded after commencement of treatment.

5. Achievement of an adequate EULAR response after 3 to 9 months of starting anti –TNF (≥20% improvement in DAS 28)
6. Regular recording of DAS 28 scores during treatment.

Statistics

Non parametric statistics were used throughout the analysis

Results

Fifty patients were commenced on biologics from March 2010 to June 2011 (16 months).

of these patients, 28 (56%) suffered from RA, diagnosed according to the 1987 American College of Rheumatology Criteria. These latter patients were included in the study. Twenty two (44%) patients were excluded from the study. These included those patients who were treated with biologic treatment for conditions other than RA such as Ankylosing Spondylitis, Psoriatic Arthritis and Juvenile Idiopathic Arthritis and those patients who had incomplete data recorded in the hospital notes because the patients were also visiting their rheumatologist in clinics outside the hospital.

Four patients did not start treatment, despite having a biologic treatment prescribed. These were patients who after appropriate counselling about potential side effects of anti–TNF therapy refused the treatment.

Two further patients were excluded from the study because they were already on biologic treatment prior to settling in Malta.

This left us with 22 patients eligible for the audit.

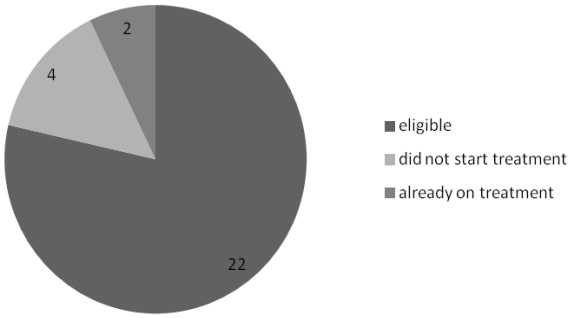

Figure 1*: Number of patients who suffered from RA and were enrolled in the study*

Recommendation 1

Biologic therapies are recommended as options for treatment of adults with the following characteristics:

A. Active RA as measured by DAS 28 ≥ 3.2

B. Have undergone trial of two DMARDS including methotrexate (unless contraindicated). A trial being defined as at least two DMARDs usually given concurrently over a 6 month period with 2 months at standard doses

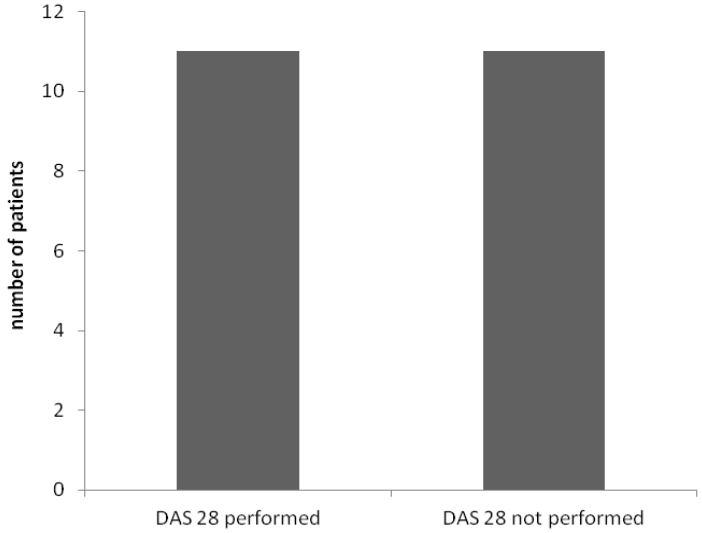

Figure 2*: Number of patients who had DAS 28 performed before starting treatment*

Results:

Of the 22 patients included in the audit, 11 patients had a DAS 28 performed prior to starting biologic therapy.

All 11 patients had DAS scores >3.2

Initial control of disease activity with at least two DMARDS at standard doses was seen in 91% of patients.

Recommendation 2

Treatment should be continued if there is an adequate response to treatment following the first 6 months of continuous treatment. An adequate response is defined as a good or moderate EULAR response.

Results:

Four patients had a DAS 28 score performed within 3 to 9 months of starting treatment. Of these 4 patients only 2 patients had a DAS 28 performed before starting treatment. Thus the EULAR response criteria could only be measured in the latter 2 patients. Both patients had a moderate EULAR response (Figure 3).

	DAS-28		
Change in DAS-28	>5.1	≤ 5.1 and >3.2	≤3.2
>1.2	Moderate	Moderate	Good
>0.6 and ≤1.2	None	Moderate	Moderate
≤ 0.6	None	None	None

Figure 3 *- The EULAR response criteria* [5]

Recommendation 3

After initial response, anti TNF treatment in RA should be monitored with assessment of DAS 28 no less frequently than 6 monthly. Anti TNF therapy should be withdrawn if an inadequate response is seen despite 6 months of continuous therapy

Results:

Of the 22 patients suffering from RA who were started on biologic agents only 2 patients had continuous monitoring as recommended (Figure 4).

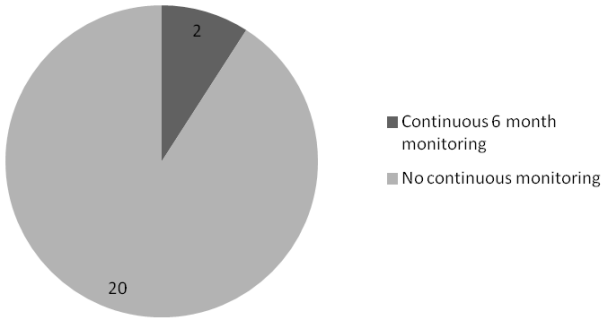

Figure 4*: Number of patients who had continuous DAS 28 monitoring during treatment*

Discussion

Biologic drugs represent an exciting advance in the treatment of RA. The response to biologics is not uniform or universal. Generally 20% of patients experience a 60% improvement in DAS28 while 60% of patients will experience a 20% improvement in the same score. Some patients fail to respond altogether and early recognition of these patients is important as these drugs are very expensive (approximately 10,000 euro per patient per year) and have potentially serious side effects particularly infection. Treatment of patients who respond to treatment is long term so the cost is ongoing. These drugs are an important resource which has to be used appropriately, judiciously and effectively.

Use of the DAS 28 to commence, change or stop biologic therapies in RA is to a degree controversial. While we have no better gold standard at present, there is concern that DAS 28 fails to measure metatarsophalangeal joint involvement given that these joints are commonly involved in the disease process. Also, the subjective criterion (patient well-being) and joint tenderness (by perhaps applying firmer pressure to the joints) can greatly skew the result obtained. Therefore intra- and inter-reliability of measurement can be significant.

In contrast to the BSRBG recommendations on eligibility criteria for first biologic which include a DAS 28 score ≥3.2, the National Institute of Health and Clinical Excellence (NICE) have an entry level for biologic therapy in RA of 5.1. The BSRBG suggest that this is an arbitrary level which is driven by economics rather than purely patient needs. The group argues that a patient with a DAS28 of, for example, 4.8, is just as likely to have disease progression but would not be eligible for biologic therapy.

It is clear from this audit that we are not adhering to the above recommendations in our Department.

Some reasons for this include:

1. DAS 28 calculator not readily available at out-patients;
2. The high turnover of staff in the department - doctors working in the department for only a few months are not adequately trained to perform DAS 28 scores.
3. Few of the permanent staff have had formal training in DAS 28 measurement techniques to reduce intra- and inter- observer variability.
4. Time constraints including difficulty in scheduling appointments in line with recommendations (at least 6 monthly intervals). Current first available follow up appointments for most of the consultants is greater than 6 months.

Recommendations following audit

1. A proforma is being developed to ensure that all RA patients have a baseline DAS score and prior non biologic DMARD history recorded prior to commencement of biologic therapies.
2. Plans are in hand for a biologic clinic to be set up to allow better scheduling of appointments for patients on biologics and improve detection of potential adverse reactions. This will complement the imminent commencement of an early arthritis clinic for detection of persistent inflammatory arthritis.
3. Training of all staff in the Department caring for patients on biologics to standardize performance of the DAS 28 and consequently minimize inter- and intra- observer variation.
4. Regular review of patients on biologic therapies to identify patients who have an inadequate response to biologics according to BSR and EULAR criteria. In these patients switching of a

biologic or withdrawal of biologic would lead to more effective and efficient use of resources.

Acknowledgments

The authors thank Dr. F Camilleri Vassallo, Dr. B Coleiro and Dr. PJ Cassar for their consent to study their patients. Thanks also to Mrs. D Aquilina and Mrs. L Grech for allowing access to their respective biologic database.

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Acyclovir induced nephropathy – A case report

Cecil Vella

Abstract

Acyclovir is frequently used in the management of suspected or proven serious viral infections in children. Despite its good safety profile serious side effects are known to occur. We describe a case of suspected viral encephalitis treated with intravenous acyclovir and complicated by acute, reversible, renal failure. To our knowledge this is the first such report in a Maltese Paediatric patient.

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Key Words
Acyclovir, crystal deposition, acute renal failure

Introduction

Acyclovir is an effective antiviral drug. Its use is particularly important in proven or suspected Herpes or Varicella infections. Reports of adverse effects are uncommon and occur almost always in adults, with renal dysfunction and neurotoxicity being the most frequently reported.[1] Adverse effects have been reported with both oral and intravenous administration of acyclovir as well as with slow or rapid intravenous administration of the drug.[2] Adequate hydration is essential with acyclovir therapy to reduce the risk of drug induced renal damage. We report a case of non-oliguric acute renal failure with complete recovery in an eleven year old boy treated with acyclovir.

Case report

An eleven year old, previously well boy, presented to casualty following a prolonged first seizure. The patient remained confused and agitated in the postictal phase with a Glasgow coma scale (GCS) of 6. He had a mild viral-like illness in the preceding days. He was afebrile on admission. There were no rashes and as the patient was unconscious neck stiffness could not be assessed. Due to persistent irregular breathing the patient was transferred for further monitoring to the intensive care unit. A computerised tomography (CT) scan of the brain was normal as were initial biochemical and haematological investigations. No contrast was administered during the CT examination. Serum creatinine level on admission was 40umol/l. In view of the prolonged seizure a provisional diagnosis of suspected viral encephalitis was made and the patient was started on triple therapy with ceftriaxone, clarithromycin and acyclovir at a dose of 500mg/m^2/8 hourly. A lumbar puncture was postponed in view of the prolonged loss of consciousness. Fluid replacement was restricted to sixty percent of requirements in view of the possible encephalitis. Twelve hours post admission the patient's level of consciousness improved. He was alert and no longer confused and was transferred to a general paediatric ward for further management. On day three post admission a routine renal profile revealed a serum creatinine level of 364umol/l. Electrolytes were normal and urea rose to 11.8mmol/l. Urine output remained good and blood pressure was on the 97th. Percentile for age. At this stage the possibility of acyclovir induced acute renal damage was considered. Renal ultrasound examination was normal. Examination of the urine under polarized light could not be performed as the investigation was not available locally. Hyperhydration (3 liters/m^2/day) and diuretics (frusemide 1mg/kg/eight hourly) were started and a urine output of 4-6ml/kg/hour was maintained. Creatinine levels increased to 450umol/l and subsequently 552umol/l on day two and three respectively. An elevated blood pressure was

treated with nifedipine 5mg twelve hourly. Acid base balance and electrolytes remained within normal. Following a maintained high urine output the patient's creatinine level started to decrease from the end of day three. By day five his creatinine level had decreased to 99umol/l, blood pressure normalised and his intravenous fluids were stopped. Outpatient review at three, seven and ten days following discharge was normal. Long term follow-up at three and six months did not reveal any abnormalities and renal function remained normal.

Discussion

The pharmacokinetics of acyclovir in children and adolescents are similar to those of adults.[3] Acyclovir is generally well tolerated. Adverse effects associated with acyclovir in children and adults include nausea and/or vomiting (2-8%), diarrhoea (0.3-4%), headache or malaise (0.6-12% of patients), asthenia or paraesthesia (0.8-2%), and skin rash (0.3-2%). Additional adverse effects associated with intravenous infusions of acyclovir include local inflammation or phlebitis (9%), transient neutropaenia (3%), elevations in serum creatinine or urea (5-10%), and elevation of hepatic transaminases (1-2%).[4,5] Recommended dosing regimen for children is 500mg/m^2/eight hourly given by intravenous infusion over a one hour period. The kidney accounts for 75-80% of the total clearance of Acyclovir. In addition, acyclovir is relatively insoluble in the urine, particularly in the distal tubular lumen, where urine flow is sluggish. These characteristics explain why intravenous infusion of acyclovir may cause intra-tubular precipitation of crystals in the kidney.[(6)] Adequate hydration is essential with intravenous use of acyclovir. Our patient was suspected of having viral encephalitis and his fluid replacement was restricted to sixty percent of requirements. This undoubtedly would have contributed to the crystallization and deposition of the drug in the renal tubules.

Risk factors for acyclovir *Nephrotoxicity* include high blood concentration of acyclovir caused by doses greater than 1500mg/m^2/day, rapid intravenous administration, pre-existing renal disease, dehydration and associated use of other nephrotoxic drugs.[7] Nephrotoxicity usually is a self-limiting condition that resolves with discontinuation of the drug and hyperhydration (3 liters/m2/day). Severe cases of renal failure may need hemodialysis. The risk of nephrotoxicty can be minimized by ensuring adequate hydration and a high urine flow and by giving acyclovir as a slow infusion rate over one hour.[8] In patient with pre-existing renal disease, acyclovir dosage should be modified according to creatinine levels.

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Endoscopic ultrasound in the staging of gastrointestinal luminal malignancies

Neville Azzopardi

Abstract

Endoscopic ultrasound (EUS) is an important tool in the staging of gastrointestinal cancers. This review highlights the use of EUS in the staging of gastrointestinal luminal malignancies and compares the performance of EUS with other imaging modalities (CT, MRI and PET-CT) in the staging of these malignancies. Management algorithms in the staging of these malignancies are also presented.

Keywords

Endoscopic Ultrasound, Oesophageal Cancer, Gastric Cancer, Rectal Cancer

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Introduction

Endoscopic Ultrasound (EUS) allows accurate T staging of gastrointestinal luminal malignancies, which is essential to plan the optimal strategy to treat these tumors. EUS is usually carried out after other imaging modalities (CT scan, PET-CT or MRI) have excluded the presence of distant metastases or when an equivocal lymph node on PET-CT needs cyto-histological confirmation of invasion. Different EUS endoscopes are available. Radial echoendoscopes give the best identification of the different layers of the intestine and at frequencies of 7.5 and 12 MHz allow a penetration of 8cm and 3cm respectively. Mini-probes are able to distinguish the different layers with greater accuracy in view of their higher frequencies (20 MHz). The depth of penetration is lower at higher frequencies but miniprobes provide greater resolutions that are ideal for evaluating early-stage cancers. The linear echoendoscope allows the acquisition of samples for cytology or histology and is needed when Fine Needle Aspirates (FNA) of lesions are planned.

A Pubmed search using the terms *oesophageal cancer, gastric cancer, rectal cancer and endoscopic ultrasound* was carried out. Studies comparing accuracy, sensitivity and specificity for T and N staging of EUS with the accuracy, sensitivity and specificity of other imaging modalities (CT, MRI, PET) were analyzed. Mangement algorithms based on established guidelines will be presented.[1,2]

Oesophageal Cancer

Oesophageal cancer is associated with a poor prognosis. In a pan-European study which analysed 5,499 patients with oesophageal cancer from 24 countries there were 1- and 5-year survival rates of 33.4% and 9.8% respectively.[3] Staging in oesphageal cancer (Table 1)[4] allows the identification of the optimal treatment strategy in this condition.

Staging for esophageal malignancy requires Computed Tomography (CT – for the identification of distant metastases) and EUS (for T and N staging). Tumor stage is predictive of surgical resectability. The most important role for EUS is in the initial triage of patients to decide who should receive neoadjuvant chemo/radiotherapy and who would benefit from immediate surgical resection. Patients with any nodal involvement typically receive preoperative neoadjuvant therapy, while patients with T1 or T2 tumors (without nodal involvement) undergo immediate surgical resection. The high-frequency EUS mini-probe can accurately detect intramucosal cancer in 70-88% of patients and submucosal invasive cancer in 83-94% of patients.[5]

Initial overall stage by EUS, the presence of LN metastases, and the presence of celiac adenopathy are all predictive factors of survival.[6] Studies have shown better survival in patients with few or no suspicious regional LN on EUS.[7] The median survival rates were 66 months for no regional LN, 14.5 months for 1-2 LN, and 6.5

months for >2 suspicious LN.[7] Since the number of suspicious periesophageal LN detected by EUS is inversely associated with survival in patients with esophageal adenocarcinoma, N staging is very important before surgery. For this reason, the Surveillance, Epidemiology, and End Results database suggests that tumor length and number of LN should be routinely reported as part of the staging system.[8]

The management algorithm for esophageal cancer is described in Figure 1.[9]

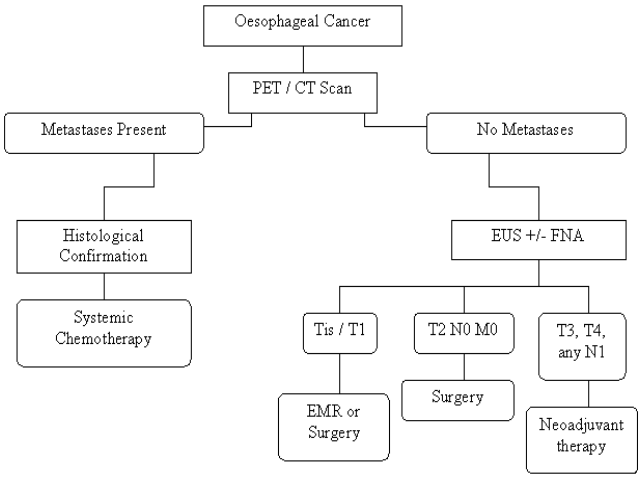

Figure 1: *Management of Oesophageal Cancer – from staging to treatment (PET- Positron emission tomography; CT Scan-Computed tomography scan; EUS +/- FNA-Endoscopic ultrasound with or without Fine Needle Aspiration; Neoadjuvant therapy – Chemo/Radiotherapy)*[7]

Once passage with the echoendoscope through the stricture is possible, staging of esophageal cancer is done by inspecting the liver, celiac axis and gastrohepatic ligament for the presence of liver or LN metastasis. The esophageal lesion and the mediastinum are then examined to identify depth of invasion and peritumoral and mediastinal adenopathy.[7] EUS is also important in restaging after patients receive chemo/radiotherapy. However, EUS is not accurate after neoadjuvant chemo/radiotherapy since it is unable to differentiate tumor from necrosis or inflammatory reaction.[10] Other studies however indicate that EUS and EUS-guided FNA can be helpful in identifying residual tumor in the LN after preoperative chemo/radiotherapy in patients who may benefit from surgery.[11]

EUS is superior to CT scan in tumor (T) staging of esophageal cancer. Thirteen studies of patients with esophageal cancer undergoing EUS showed 71-100% sensitivity and 67-100% specificity while 5 studies in patients undergoing CT scan showed 40-80% sensitivity and 14-97% specificity.[12] N staging also appears to be superior with 60-97% sensitivity and 40-100% specificity for EUS versus 40-73% sensitivity and 25-67% specificity for CT scan.[12] In addition, FNA of suspicious LN allows cytological confirmation of malignancy. The sensitivity in staging LN increases from 71% with EUS to 83% with EUS-FNA.[13] EUS also appears to be superior to PET in T staging and in detecting peritumoral and celiac LN.[14] FDG-PET has a 15% false-positive rate in the detection of distant and hematogenous metastases.[14] EUS FNA can be used to confirm positive findings on PET scans.[15]

The combination of CT, PET and EUS decreases the number of unnecessary operations by half when compared with CT alone.[14] Detection of previously unidentified celiac axis metastases intraoperatively also decreased significantly when CT was combined with PET or EUS. EUS also detects occult liver metastases, though it visualizes only the medial two thirds of the liver. FNA can be performed for histological confirmation of liver metastasis.[16]

Gastric Cancer

Gastric cancer is the second leading cause of cancer related deaths worldwide.[17] Accurate staging of gastric cancer (Table 1) by determining tumor extent and nodal involvement is important in the treatment algorithm (Figure 2).

Table 1: *American Joint Committee on Cancer TNM Classification for Esophageal and Gastric Cancers*[2]

Oesophageal Cancer	
T Stage	
Tx	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Invades lamina propria or submucosa
T2	Invades muscularis propria
T3	Invades adventitia
T4	Invades adjacent structures
N Stage	
Nx	Regional nodes cannot be assessed
N0	No regional LN metastasis
N1	Regional LN metastasis
M Stage	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Gastric Cancer	
T Stage	
Tx	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Invades lamina propria or submucosa
T2	Invades muscularis propria or subserosa
T3	Penetrates serosa without invasion of adjacent structures
T4	Invades adjacent structures
N Stage	
Nx	Regional nodes cannot be assessed
N0	No regional LN metastasis
N1	Metastasis in 1-6 regional LN
N2	Metastasis in 7-15 regional LN
N3	Metastasis in >15 regional LN
M Stage	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

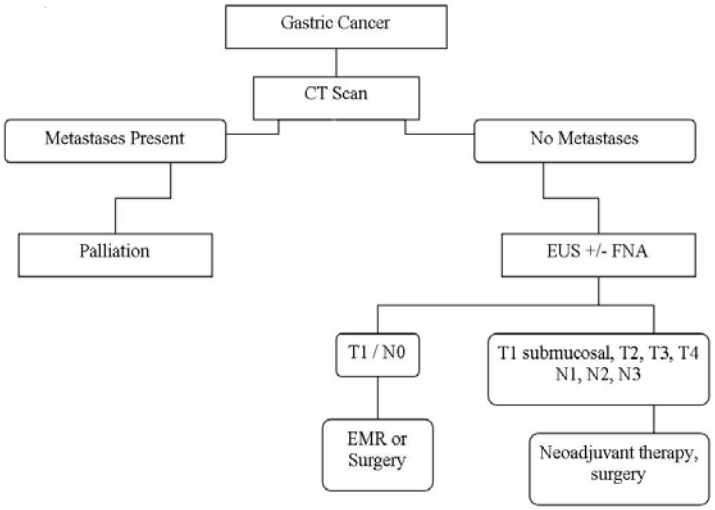

Figure 2: *Management of Gastric Cancer – from staging to treatment (CT Scan-Computed tomography scan; EUS +/- FNA-Endoscopic ultrasound with or without Fine Needle Aspiration; EMR-Endoscopic Mucosal Resection; Neoadjuvant therapy - chemotherapy)*[27]

Evidence shows that 5-year survival rate for early gastric cancer confined to the mucosa or submucosa is >75% following resection but < 30% with distant metastasis or with the involvement of >15 (N3) LN.[18]

Surgery is the recommended treatment of choice for localized gastric cancer with endoscopic mucosal resection (EMR) reserved for cancers limited to the mucosa. Neoadjuvant chemotherapy is recommended for patients with deeper invasion. CT is important to exclude distant metastases but lacks accuracy in T and N staging of gastric cancer[19], while EUS has much greater accuracy in evaluating the depth of invasion of primary gastric cancer.[19-21] In addition, EUS-guided FNA of LN adds to the accuracy of nodal staging.[21]

The overall sensitivity of EUS in determining T stages is best for T1 and T3 lesions, whereas EUS is least accurate for T2 and T4 lesions. In a meta-analysis of 54 studies carried out between 1988 and 2010, the pooled sensitivity was 83% for T1 lesions, 65% for T2, 86% for T3, and 66% for T4 lesions.[22] This is believed to occur because identifying T1 and T3 invasion is facilitated by the hypoechogenicity of the muscularis mucosa and muscularis propria while identifying T4 invasion is made difficult by the limited depth of penetration of the ultrasound waves. The pooled sensitivity for N staging was 69% with a specificity of 84%.[22] In situations where malignant LN can be difficult to distinguish from benign nodes, EUS-FNA cytology and biopsy may offer better diagnostic yields.

A systematic review comparing the diagnostic T stage accuracy of EUS with CT revealed an accuracy of 65-92% with EUS and an accuracy varying between

77.1-88.9% with CT.[23] Another review comparing N stage sensitivities and specificities of EUS with CT showed that EUS had 71% sensitivity and 49% specificity while CT had 80% sensitivity and 78% specificity.[24] CT is also superior in detecting distant metastasis and both techniques are complementary for overall staging. EUS is required in the absence of distant metastases since management decisions will then depend on the depth of invasion.

Better surgical outcomes are obtained in patients with locally invasive gastric cancer who receive preoperative neoadjuvant chemotherapy. However, following chemotherapy, the accuracy of CT and EUS for both T and N staging drops significantly (57% and 47% for T staging and 37% and 39% for N staging).[25] EUS is more sensitive than transabdominal ultrasound, CT and laparoscopy for the detection of intraperitoneal fluid, which is usually indicative of incurable disease. EUS-FNA of low-volume ascites can be performed safely.[26]

Visualisation of gastric lesions during EUS is facilitated by aspiration of air and instillation of de-aerated water into the stomach to submerge the lesions completely, thus allowing better acoustic coupling. With the standard echoendoscope, five distinct layers are seen, with 3 hyperechoic alternating with 2 hypoechoic layers. The first 2 layers represent the mucosa, the third layer represents the submucosa, the fourth layer is the muscularis propria and the last layer is the serosa. Table 1 describes the T staging of gastric cancer. Tumors confined to the mucosa can be treated with EMR while those involving the submucosa carry a 20% risk of LN involvement and therefore require surgery.[27]

Perigastric and regional (celiac axis, gastrohepatic ligament) LN are next assessed (Figure 2). Suspicious LN features during endosonography include hypoechogenicity, sharp borders, round shape and size >10mm. All 4 features are present in only 25% of malignant LN, and FNA of nodes with any of these features is necessary to confirm or exclude malignancy.[28] Distant metastasis (M) staging by checking the left lobe of the liver, the peritoneum, the pleural layers of the lung, and mediastinal LN is the final step. The finding of malignant ascites, pleural effusion and malignant mediastinal nodes is an indication for neoadjuvant or adjuvant treatment.[29]

Rectal cancer

Rectal cancer represents 5% of malignant tumors and is the fifth commonest cancer in adults.[30] Staging of rectal cancer identifies patients with locally invasive tumors who should be treated with neoadjuvant therapy before surgery (Figure 3).

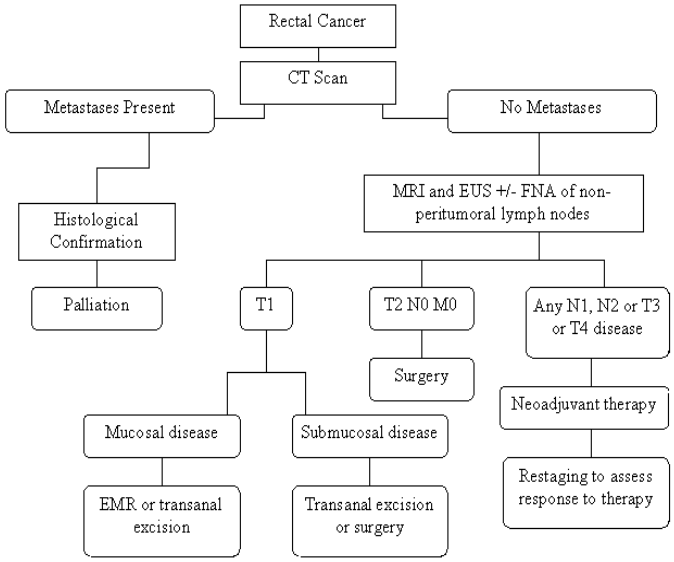

Figure 3: *Management of Rectal Cancer – from staging to treatment (CT Scan: Computed tomography scan; EUS +/- FNA: Endoscopic ultrasound with or without Fine Needle Aspiration; EMR: Endoscopic Mucosal Resection; T1-Tumor invades lamina propria or submucosa; T2: Tmor invades muscularis propria; T3-Tumor penetrates serosa; T4-Tumor invades adjacent structures; N0 – No regional lymph node metastases; N1 – Metastases in 1-3 regional nodes; N2 – Metastases in 4 or more regional nodes; M0 – No distant metastases; Neoadjuvant therapy – chemotherapy and radiotherapy)*[29]

The accuracy of EUS for T staging in rectal cancer is 85% while the accuracy for N staging is 75%. With the addition of FNA of LN, accuracy increases to 87%.[31] During EUS staging of rectal cancers, the relationship of the tumor with adjacent organs such as the prostate, bladder, and seminal vesicles in men and the bladder, vagina, cervix and uterus in women is assessed. The perirectal area is studied for the presence of suspicious LN or involvement of the iliac vessels.

Rectal cancer is seen as a hypoechoic lesion that disrupts the rectal wall pattern. A tumor limited to the submucosa is classified as T1, while if it invades the muscularis propria, it is classified as T2. T3 tumors penetrate into surrounding fat while T4 lesions invade into adjacent organs. Both radial and linear EUS scopes can be used for staging rectal lesions; however FNA of lymph nodes can only be done with the linear scope. High-frequency mini-probes using the water-filling technique may be a better option for small lesions (<1-2 cms). Alternatively, changing the patient position may allow better visualization of the lesion.

EUS is superior to CT and MRI for T staging of rectal tumors. In a meta-analysis (5000 patients), CT accurately T staged the tumor in 73% of cases and had accurate N staging in 22-73%.[32] MRI also has poor

accuracy in T staging of rectal cancer (52-54%).[33] A meta-analysis (42 studies) evaluating EUS in rectal tumors revealed sensitivities and specificities of 88% and 98% for T1, 81% and 96% for T2, 91% and 96% for T3 and 95% and 98% for T4 tumors.[34] This increased accuracy translates into improved patient management with more patients undergoing neoadjuvant treatment with chemotherapy and radiotherapy before surgery and a more cost-effective strategy when combining initial abdominal CT (to exclude distant metastases) and EUS (for local staging).[35]

N staging with EUS has not been shown to be superior to other imaging modalities. The pooled sensitivity and specificity of EUS in diagnosing nodal involvement in rectal cancers were 73% (95% confidence interval [CI] 70.6-75.6) and 76% (95% CI 73.5-78.0) with a pooled diagnostic odds ratio of 7.87 (meta-analysis of 35 studies), which is similar to the accuracy of CT and MRI.[36] However, FNA of suspicious lymph nodes improves accuracy to 87%.[37] Benign perirectal nodes are not usually visualized by EUS. Therefore, finding perirectal nodes during EUS is sufficient to warrant sampling by FNA.

Conclusion

With its high sensitivity and specificity in tumor (T) staging, endosonography has become an essential tool in the staging of gastrointestinal luminal malignancies. EUS is also important in lymph node (N) staging as it allows FNA cytological sampling of suspicious nodes. However, distant metastases (M staging) should be excluded by abdominal and thoracic computed tomography (with or without PET) before EUS is carried out.

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Motor Neurone Disease (MND) among Maltese in Malta and Australia is not linked to Poliomyelitis

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Abstract

To link death from motor neurone disease/amyotrophic lateral sclerosis (MND /ALS) with previous paralysis of poliomyelitis. The forebearers (parents, grand-parents, etc) of 196 Maltese with MND, who have died in Malta and Australia, were compared with records of 1072 Maltese with paralytic poliomyelitis. There is no evidence that MND was linked to previous poliomyelitis.

Keywords

amyotrophic lateral sclerosis, Australia, consanguinity, Malta, motor neurone disease, poliomyelitis.

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Introduction

There have been reports that past poliomyelitis might be a risk factor for motor neurone disease (MND), but proof has been lacking [1] and Armon et al have called for more studies. [2.] Poliomyelitis and MND have shared symptoms, the motor neurones affected are similar in both diseases and the incidence in males is about 1.5 times greater than in females. Latent enteroviral infections have been (rarely) reported, but without MND symptoms. [3] Some studies have reported finding enterovirus RNA in MND specimens, but this has been probably due to laboratory cross contamination.[4]

In Malta very few death certificates recorded MND before 1990, but reports have increased since the appointment of consultant neurologists. When infant mortality fell dramatically in the late 1940's, Maltese were encouraged to emigrate, especially to Australia. As poliomyelitis in Malta occurred in children whereas MND usually occurs in late middle age, in most countries it is difficult to match occurrence of both diseases in the same person. It is possible to do so in Malta because many hundreds of cases of polio occurred in young children before the 1950's and who are now of an age when MND is common.

Methods

This study comprises 148 Maltese whose death certificates included a diagnosis of MND: one was resident in England and two had been born in the USA, but had returned to Malta. One death in the USA and three in Britain were found from Maltese newspapers. The two earliest births were in 1898 and the latest was in 1979 (he died at the age of 20). The Health Information Unit (Malta) kindly supplied verified deaths from MND since 1990 and Dr. Geoffrey Dean provided some earlier ones. State registries in Australia sent photocopies of forty eight born in Malta who had been emigrants to Australia and whose deaths were certified as MND.

In 1985 the names of 1,072 Maltese children diagnosed with poliomyelitis were traced in the records of the Infectious Diseases Hospital and traced their parents, as well as those of baptism-matched controls. Marriages and births were traced in parish registers and the Public Registry, but registering marriages was voluntary until 1979 and probably about 10% were unregistered before 1900 and perhaps about 5% since then.

Results

MND and past poliomyelitis only 34 cases of polio were found before the 1942 epidemic. These 34 and most of the nearly 1,000 other polio cases born before their paralysis in 1950 had reached the age of 64 or older by 2010.[6] The median age at death of both males and females for MND was 64 yr for those dying in either Malta or Australia, with the majority close to the median although the range was from 20 to 90 yr. If poliomyelitis is a risk factor for MND, many of the Maltese polios would have died of MND. None has done so yet.

There was little evidence in this study to link the two diseases. MND158 was the father of polio 859 and the control C 321. Polio 179 and MND 110 were sibs as were polio 981 and MND 127. It is possible that MND's might have more and closer links to polios than to controls (of the polios). Similarly, villages with many polios might be centres of MND incidence. In one village on the smaller island of Gozo there were 29 polio cases, with 23 related in one compact consanguineous family group, but the six others were not related to them. From the same village, there were four MNDs, two others with fathers of MNDs and two with a great grand-parent of an MND, but none was related to the polios.

There were a number of closely related polios in one village, but there were no MNDs there. In another area of several villages, there were closely related polios who were not related to a group of related MNDs in the same villages. Although the polios appear to be unrelated to the MNDs, it might be that individual polios and MNDs were closer to each other than to controls. The MNDs showed links to parents of two polios, 19 grand-parents and 21 great grand-parents of polios whereas the controls had links to five, 24 and 18 respectively.

Conclusion

This study and some others have found no evidence that previous poliomyelitis is linked with subsequent MND. [7, 8.] One or two cases of MND occur in every 1,000 deaths, so that we may expect one or two to eventually occur with a MND having had polio. This will be coincident, not causal. The two diseases are different with different causes, even though they target the same cell – the motor neurone.

The data on cards, medical records, computer print-outs and notes etc will be deposited in the Melitensis Collection of the University of Malta. The Medical Ethics Committee of Malta had 'no objection to this study'.

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Amyand's hernia: a case report

Peter Muscat

Abstract

The presence of vermiform appendix, whether normal or inflamed in the inguinal hernia, is referred to as Amyand's hernia. This is rare occurring in about 1% of inguinal hernias in adults.[1] This is a report of Amyand's hernia, which presented as a component along with partially necrotic omentum with metastasis in a 75 year old male patient. Appendicectomy followed by hernia repair using synthetic mesh was performed with an uneventful recovery.

Key words

Amyand's hernia, appendix, strangulated inguinal hernia, metastasis

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Introduction

Claudius Amyand (1680 -1740) was surgeon to King George II and principal surgeon at St George's and Westminster hospitals of London. He performed the first recorded successful appendicectomy on an 11 year old boy with a perforated appendix within an inguinal hernia sac in 1735.[2]

Case report

A 75 year old man presented at the emergency department with a right inguinal swelling present for the previous three weeks. The swelling was initially reducible, however it became irreducible two days prior to admission to hospital. He gave a history of right sided abdominal pain over the past two days with no symptoms related to the gastrointestinal or urinary tracts. On examination the patient had a tender, non reducible mass over the right inguinal region. A full blood count showed a haemoglobin of 11.4gm/dl and leucocyte count of 15 x 10 9/L. Renal function and liver function tests were normal.

Two months prior to this event, the patient presented with melaena. Apart from being a heavy smoker, the patient did not have any relevant past medical history. Chest X-ray on admission showed a mass on the right side of the lung. Urgent CT scan of the thorax and abdomen showed consolidation in the left lung. CT guided biopsies from this lung consolidation were taken. Histology of these biopsies showed an undifferentiated lung carcinoma. Gastroscopy revealed a small gastric ulcer in the process of healing while colonoscopy was reported as normal.

A diagnosis of strangulated right inguinal hernia was established and the patient was scheduled for emergency surgery. At surgery, an irreducible inflammatory oedematous mass was found inside the inguinal canal. This mass was identified as the tip of the appendix adhered to the indirect inguinal hernia sac, together with partially necrotic fatty omentum. The base of the appendix did not show signs of inflammation. An appendicectomy and partial omentectomy was performed. This was followed by Lichtenstein hernioplasty using synthetic mesh. Broad-spectrum antibiotic cover was given. Postoperative recovery was uneventful and the patient was discharged home the next day on co-amoxiclav 1g bd for five days. Six weeks after discharge from hospital the patient suffered a cerebrovascular accident and died.

Histology of the appendix and omentum was reported as ' metastatic poorly differentiated neoplasm infiltrating the omentum and outer appendiceal wall'.

Discussion

The contents of a hernial sac is rarely significant in an inguinal hernia, as the sac usually contains the omentum or small bowel. However, there can be surprising contents such as Meckel's diverticulum (Littre's hernia), portion of the circumference of the intestine (Richter's hernia), bladder (sliding hernia) or appendix (Amyand's hernia).[3] Literature search on Amyand's hernia with metastatic involvement is very scanty. A literature search from Medline resulted in only one documented case report of Amyand's hernia containing adenocarcinoid tumour of the appendix.[4]

The clinical presentation in Amyand's hernia is very similar to that of a strangulated hernia with local peritonism. It is rare to be able to diagnose Amyand's hernia pre-operatively. Pre-operative computed tomography (CT scan) of the abdomen may be helpful but we do not perform CT scans routinely for an irreducible hernia.[5] CT scan provides only indirect clues and diagnosis is almost always done intraoperatively.

The aetiology of Amyand's hernia is often questioned in literature.[6] A possible explanation could be that due to herniation, the appendix becomes more vulnerable to micro-traumatism. Following this, fibroses develops and the appendix gets adherent to the hernial sac. Muscle contractions and changes in abdominal pressure may cause compression of the appendix, resulting in decreased blood supply and secondary bacterial inflammation.

There is no standard protocol for the management of Amyand's hernia. Important determinants for appropriate surgery include the presence of an inflamed appendix, contamination of the surgical field, patient age and anatomic features.[7] A normal appendix can be returned back to the peritoneal cavity or alternatively appendicectomy can be performed.[7] There is no clear consensus on mesh repair. Hernioplasty (mesh repair) without appendicectomy is a favoured option in patients with a normal appendix.[9]

In our case report transherniotomy appendicectomy with partial omentectomy followed by mesh repair was performed without any post-operative complications, with broad spectrum antibiotic cover. In cases of appendicitis transherniotomy appendicectomy should be performed followed by herniorrhaphy (sutured repair).[9,10] The presence of pus or perforation is an absolute contraindication to mesh repair.[10]

Conclusion

Appendicitis within an Amyand's hernia is rare, and when it occurs it is usually misdiagnosed as strangulated inguinal hernia. This also represents a surgical emergency. Early operative intervention is the mainstay of successful management of Amyand's hernia. Awareness of this disease and its misleading clinical presentation is of utmost importance as most of these cases are diagnosed intraoperatively.

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Audit on the use of radiological investigations in the management of rhinosinusitis

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Abstract

Objectives: The aim of this audit is to establish the cost to the Maltese health system from the use of radiological imaging in managing rhinosinusitis and to identify areas in which these costs can be minimised by following guidelines on the management of rhinosinusitis.

Methods: All plain radiographs and computed tomography scans (CT) of the paranasal sinuses requested in the Mater Dei Hospital over a one year period were analysed. Data was collected regarding: the quantity of investigations ordered, age of the patients, cost and requesting department.

Results: Over one year: 205 CT scans and 113 sets of plain radiographs of the paranasal sinuses were requested, costing a total of euro103,440. The majority (73%) were elective requests made by ENT consultants. Five percent of CT scans were requested for patients less than 10 years of age.

Conclusion: Rhinosinusitis is diagnosed clinically, only requiring radiological investigation in more complex cases best managed by specialists in ENT. Plain radiographs have limited use in the management of rhinosinusitis. Judicious use of imaging requests whilst following clinical guidelines is required to save money and minimise patient exposure to ionising radiation.

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Key Words

Sinusitis, Clinical Audit, X-Ray Computed Tomography

Introduction

Acute and chronic rhinosinusitis are very common conditions faced by the otolaryngology (ENT) department in Mater Dei Hospital (MDH), affecting 15% of the population in Western countries.[1] Sinusitis refers to the inflammation of the mucosa lining the cavities of the paranasal sinuses and is often accompanied by inflammation of the nasal mucosa, hence the term rhinosinusitis. Patients commonly present with symptoms of nasal blockage, nasal discharge, facial pain and anosmia. Rhinosinusitis is commonly classified into either being acute or chronic according to the duration of symptoms, with acute rhinosinusitis said to last less than 12 weeks and chronic rhinosinusitis longer than this.[2]

The diagnosis and management of rhinosinusitis requires clinical acumen, and on occasion, benefits from the judicial use of radiological imaging. Despite the advancements seen in diagnostic imaging, the diagnosis of sinusitis is still a challenge. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 recommends that no diagnostic imaging is required for acute rhinosinusitis in adults and children, with the diagnosis being made clinically.[2] Computed Tomography (CT) scanning is however recommended if there are difficulties in management such as: signs of complications, in severe disease or in

immunocompromised patients. Patients with these complications and those who are being considered for surgery should ideally be managed by a specialist in ENT and be examined endoscopically prior to ordering further investigations. CT is indicated prior to performing endoscopic sinus surgery as it is essential to assess the individual anatomy of the paranasal sinuses. Plain radiographs are of limited diagnostic use, having been largely superseded by CT scanning owing to the greater definition of the paranasal sinuses that it provides.

Accompanying the rising incidence of this common condition is the financial burden arising from the radiological investigations used in its diagnosis and management. In this relatively inauspicious time it is more pertinent than ever to ensure that finances dedicated to patient care are used with utmost responsibility. As well as the cost of over-investigation, subjecting patients to unnecessary ionising radiation means that patients may receive more harm than good given the limited usefulness of imaging in certain circumstances. Extra care should be taken to avoid exposing young patients (less than 10 years of age) to unnecessary ionising radiation.

The aim of this study is therefore to analyse the cost to the Maltese public health system from the use of radiological imaging in managing rhinosinusitis and to identify areas in which the use of these resources can be made more appropriate by auditing the requests made over a one year period.

Methods

Data over a period of one year was reviewed, auditing the use of imaging in the management of rhinosinusitis in MDH. All inpatient and outpatient plain radiographs and CT scans of the paranasal sinuses for patients of all ages with clinical signs of acute or chronic rhinosinusitis were analysed. The audit was conducted retrospectively for the time period from the 1st January 2009 to the 31st December 2009.

Standards

Standard 1: No plain radiographs of the paranasal sinuses should be requested to diagnose rhinosinusitis (target = zero).

Standard 2: CT scans should ideally be requested by specialists in ENT, **unless** the patient is already under the care of a non-ENT specialist and: there is very severe disease, the patient is immunocompromised or there are signs of complications (target = 100% CT scans requested by specialists in ENT).

Standard 3: No CT scans should be requested for patients of less than 10 years of age unless: there is very severe disease, the patient is immunocompromised, there are signs of complications or surgery is being considered (target = zero).

The standards of this Audit are based on clinical evidence collated and presented in The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 which provides recommendations for how rhinosinusitis should be diagnosed and managed.[2]

As well as collecting data to assess the compliance with the above standards, data was collected relating to other parameters regarding the imaging requests made. These parameters consisted of:

- the number of each imaging modality requested
- requesting department
- whether investigations were requested as urgent or elective
- the age of the patients imaged
- total cost

This information was accessed from the Radiology Information System (RIS) and from the local Patient Archive and Communication System (PACS) and recorded and analysed using Microsoft Excel. The costs of the imaging involved were obtained from the billing section of MDH.

Results

The total sample size for this audit was 318 radiological images. Two hundred and five CT scans and 113 plain sinus radiographs (consisting of three sinus views) were requested over this one year audit period (standard 1).

Requesting Department

Of the 205 CT sinus scans performed, the overwhelming majority were requested by ENT consultants (standard 2: *n*=149, 72.7%), with the remainder being ordered by the Accident and Emergency department (A&E) (*n*=36, 17.6%) or other departments (*n*=20, 9.7%) (Figure 1A).

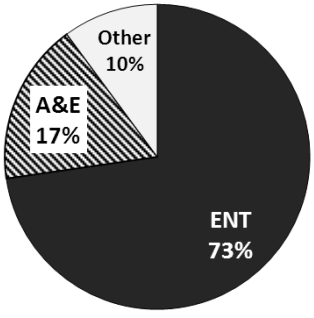

Figure 1A: *Percentage of CT scans requested by each department*

Similarly, of the 113 plain radiograph series requested, most were requested by the ENT department (*n*=76, 67.3%) (Figure 1B).

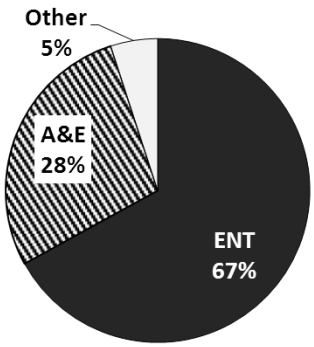

Figure 1B: *Percentage of plain radiographs requested by each department*

Elective versus Emergency

When both imaging modalities were combined (*N*=318), just over one fifth were requested as urgent (*n*=67, 21.1%), with the remainder ordered as elective investigations, mostly by ENT consultants in outpatient clinics (*n*=251, 78.9%) (Figure 2).

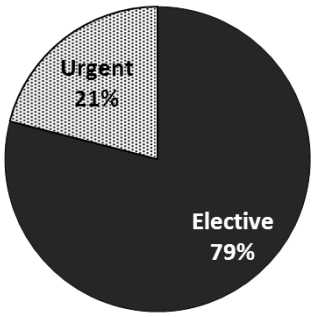

Figure 2: *Percentage of urgent or elective requests for CT and plain radiographs of the paranasal sinuses*

Patient Age

Despite the limited diagnostic usefulness of imaging in the diagnosis of sinusitis in young children and given the increased sensitivity of children to the harmful effects of ionising radiation, a relatively high amount of both CT scans (standard 3: *n*=10, 4.9%) (Figure 3A) and plain radiograph series (*n*=5, 4.4%) (Figure 3B) were requested for children less than 10 years of age.

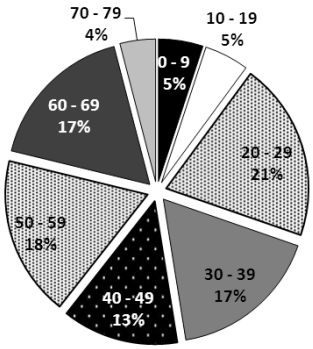

Figure 3A: *Pie chart demonstrating the age of the patients for which CT scans were requested*

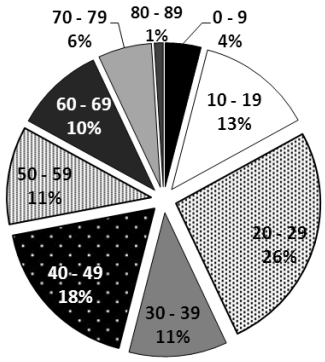

Figure 3B: *Pie chart demonstrating the age of the patients for which plain radiographs were requested*

Total Costs

For a standard plain radiograph series of 3 images, the total cost is €77. The cost of a CT scan of the sinuses at MDH is €350. The total cost to the Maltese public health system for the imaging alone over this 1-year period is therefore €7,910 for the plain radiographs and €95,530 for the CT scans, making a total of €103,440 (Figure 4). This does not take into account hidden-expenses such as the staff-time involved in carrying out the scans, nor the potential gain in using these imaging resources for the benefit of other patients.

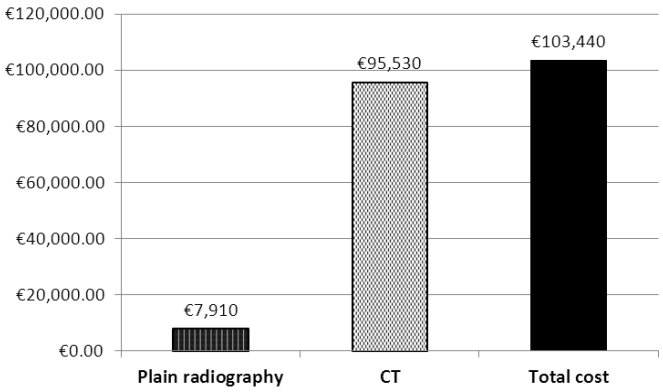

Figure 4: *Bar chart representing the cost to the Maltese health system from the use of plain radiography and CT in managing rhinosinusitis*

Standards

Standard 1: Due to the low sensitivity and specificity of plain radiographs, their use in the diagnosis of rhinosinusitis is no longer recommended. 113 plain sinus radiographs were requested over thus one year audit period. The target was zero.

Standard 2: Seventy three percent of CT scans were requested by the ENT department. The target was 100%.

Standard 3: Five percent (*n*=10) of the 205 CT scans requested were for children of less than 10 years of age. The target was zero.

Discussion

Radiological Imaging in Rhinosinusitis

Plain radiography

Plain radiography in acute rhinosinusitis may demonstrate findings of: mucosal thickening, air-fluid levels, and complete opacification of the involved sinuses. Despite findings of mucosal thickening being observed in 90 percent of cases of acute rhinosinusitis, it is a very non-specific finding.[3] Misdiagnosis is highly undesirable as it means that some patients will receive treatment unnecessarily and others with undiagnosed rhinosinusitis may go untreated. Due to the low sensitivity and specificity of plain radiographs, their use in the diagnosis of rhinosinusitis is no longer recommended.[4] For this reason CT has taken over the role of plain radiography. The current waiting time for a routine CT scan can be 2-3 months whereas plain radiography may be available the same day. Despite this, it still remains a fact that plain radiography has a low sensitivity and specificity in the diagnosis of rhinosinusitis and is unable to provide information in the complicated cases of rhinosinusitis for which a CT scan is indicated.

Computed tomography

CT scans provide much more information about the anatomy and abnormalities of the paranasal sinuses than plain films. Although more sensitive than plain radiography, CT findings are still relatively non-specific and should therefore be used in conjunction with clinical and endoscopic findings in order to avoid overdiagnosis and therefore overtreatment of patients. CT should therefore not be used routinely as a primary diagnostic step, unless there are worrying clinical features such as unilateral symptoms.[2] The diagnosis of rhinosinusitis is a clinical one, with CT imaging used to guide management in patients who are unresponsive to three months of maximal medical therapy or in complicated cases. CT is essential in assessing the complexity of the sinonasal anatomy prior to performing endoscopic sinus surgery.[5] As well as the cost associated with a CT scan of the sinuses (euro350), patients are also exposed to harmful radiation, quantified at an effective radiation dose of around 1.1mSv per investigation (approximately equivalent to 55 chest radiographs) compared to 0.07mSv for a series of three plain radiographs (approximately equivalent to eight chest radiographs).[6] This ionising effect is not insubstantial and is of particular concern in younger patients. This study found that five percent of CT scans requested were for patients less than 10 years of age. Recent interest has arisen in attempts to improve image quality whilst also reducing the radiation dose.[7]

Other imaging techniques

Magnetic Resonance Imaging (MRI) is used secondarily to CT as it has a higher cost, provides poorer imaging of bony anatomy and still produces many false-positive results. It may be used as an adjunct to CT to investigate cases of suspected neoplasia.[2] The use of sinus ultrasound is limited by its poor sensitivity and specificity. It is therefore rarely used in clinical practice.

Recommendations for the use of Imaging

The diagnosis of rhinosinusitis is a clinical one based on the following symptoms and signs:

- Symptoms of: nasal blockage/ congestion *OR* nasal discharge (including symptoms of facial pain/ pressure and anosmia).
  AND
- Signs of: polyps *OR* mucopurulent discharge *OR* mucosal oedema and obstruction, on endoscopy.[2]

Acute rhinosinusitis

According to the guidance provided by The European Position Paper on Rhinosinusitis and Nasal Polyps 2012, plain sinus radiographs are not routinely recommended in managing acute or chronic

rhinosinusitis as thickening of the sinus mucosa is a non-specific finding and may occur in asymptomatic patients. CT should not be used to diagnose acute rhinosinusitis in adults or children unless: there is very severe disease, the patient is immunocompromised or there are signs of complications, in which case the patient should ideally be managed by a specialist in ENT. The 2008 European Commission referral guidelines for imaging concur with these recommendations, advocating the use of CT in cases where maximal medical therapy has been unsuccessful or in cases where complications or malignancy are suspected.[6] If the patient is unresponsive to medical therapies, non-ENT specialists may consider referring the patient to the ENT department where the patient may be examined endoscopically prior to considering radiological investigation

Chronic rhinosinusitis

CT scanning is not recommended in the management of chronic rhinosinusitis by non-ENT specialists unless there is very severe disease, the patient is immunocompromised or there are signs of complications. Referral to an ENT specialist may be considered if medical management has not improved the patient's symptoms after four weeks or if an operation is to be considered. An ENT specialist may request a CT scan prior to making a decision to perform surgery. A navigation system used during endoscopic sinus surgery is of particular benefit as it provides real-time imaging of the sinuses as the operation progresses.

Cost and Future Audit

This study brings to light the large financial burden to the health system arising from the costs of imaging used in managing rhinosinusitis. It is the responsibility of health care professionals to ensure that clinical practice makes best use of the resources available in order to maximise the benefit to patients. This study's findings raise the need for future re-audit in this field with particular emphasis on the following audit standards:

1. Patients with rhinosinusitis should be diagnosed clinically without the use of plain radiographs or CT
2. CT scans should ideally be requested by ENT specialists
3. The number of CT scans in patients of less than 10 years of age should be minimised

In order to achieve these standards, it is important that all clinicians treating patients with suspected rhinosinusitis are aware of the guidelines regarding its management. Ways to accomplish this include: presenting the above findings at clinical meetings and publishing them to highlight the areas in the management of rhinosinusitis which may be improved.

Limitations

A potential limitation of this study is that we don't know what proportion of patients with rhinosinusitis were diagnosed clinically or by radiographic investigation as we audited all patients for whom imaging was requested. Future audit may consider looking at a sample of patients with rhinosinusitis diagnosed clinically according to the European Position Paper definition of rhinosinusitis and assess how many of these patients underwent imaging and for what purpose.

Conclusion

The diagnosis of acute and chronic rhinosinusitis is based upon a thorough history and examination. Imaging is not required to make the diagnosis and is only useful in certain situations best managed by the ENT department. The cost to the Maltese public health system from the use of imaging in managing rhinosinusitis is not insignificant (euro103,440), and a proportion of this amount may have been spent unnecessarily, with CT scans being requested which have little or no impact on the management decisions regarding the patients' symptoms. Symptoms of which are largely managed by relatively safe empirical medical therapies anyway. Careful consideration should be taken to decide, prior to requesting any investigation, how it will affect the patient's management and if it will be of benefit to them.

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Surgical excision of renal cell carcinoma with caval and intra-atrial tumour thrombus extension using deep hypothermic circulatory arrest

Simon Bugeja, Patrick Zammit, Joseph Galea, Karl German

Abstract

Surgery for tumour thrombus extension in Renal Cell Carcinoma may be associated with a good prognosis if no distant metastases are identified and if the thrombus can be completely excised. The surgical approach chosen will depend on the level of tumour thrombus extension. We present a case of Renal Cell Carcinoma in the right kidney with tumour thrombus extension into the right atrium. This was successfully removed by right radical nephrectomy and excision of the atrial thrombus using cardio-pulmonary bypass and deep hypothermic circulatory arrest. This is the first procedure of its kind to be undertaken in Malta.

Keywords

Renal cell carcinoma, Atrial tumour thrombus Surgery, Cardio-pulmonary bypass, Deep hypothermic circulatory arrest

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Introduction

Some cases of renal cell carcinoma (RCC) may be very aggressive. One of the features underlying this is their propensity for vascular invasion. Renal Vein (RV) or Inferior Vena Cava (IVC) extension occurs in 4 to 10% of cases.[1] Very rarely tumour thrombus may extend all the way above the diaphragm and into the right atrium.[2]

In 1972, Skinner *et al.* first reported that caval tumour thrombus extension in renal cell carcinoma is potentially curable if complete excision can be achieved.[3] The surgical approach chosen will depend on the level of tumour thrombus extension. The higher the level, the more complex the surgical technique becomes, often requiring a multidisciplinary approach. Careful pre-operative staging and planning of surgery is paramount to a successful outcome.

We present a case of right kidney RCC with intra-atrial tumour thrombus extension successfully treated by radical nephrectomy and excision of the thrombus from the right atrium using cardio-pulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA). This is the first procedure of its kind to be undertaken in Malta.

Case Presentation

A 59-year-old otherwise healthy male presented to the Urology Unit at Mater Dei Hospital with acute onset of right loin pain and gross haematuria. An ultrasound scan revealed a solid lesion in the lower pole of the right kidney. Further evaluation by CT Scan confirmed the presence of a large renal tumour with extension of tumour thrombus into the renal vein and intrahepatic segment of the IVC. (Figure 1a,b).

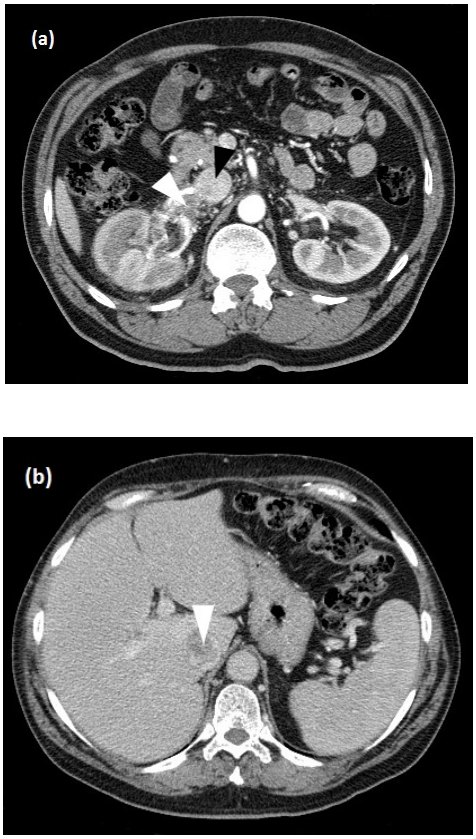

Figure 1*: CT showing (a) thrombus involving right renal vein (white arrowhead) and inferior vena cava (black arrowhead); (b) tumour thrombus in intrahepatic IVC (white arrowhead)*

Doppler Ultrasound revealed supra-diaphragmatic extension of tumour thrombus into the right atrium. There was no evidence of any other extrarenal spread or distant metastases.

Following accurate tumour staging, the surgical approach was planned in conjunction with the cardiothoracic surgical team. Tumour nephrectomy was performed via a midline laparatomy incision, giving excellent exposure of the right kidney and the IVC that was dissected up to the inferior border of the liver. The duodenum and small bowel were reflected medially off its anterior surface. The right kidney was completely mobilised on its vascular pedicle in a plane outside Gerota's fascia. A sling was placed around the renal vein while the renal artery was divided between ligatures. At this stage the cardiothoracic team performed a median sternotomy to expose the pericardium. The ascending aorta was cannulated using a reinforced straight tipped aortic cannula and the right atrium was cannulated with a Ross atrial basket. CPB was established after full heparinisation. The patient was cooled down slowly using the CPB heat exchanger and the head was wrapped in ice slush to further protect cerebral structures. When a core temperature of 16^0C was reached, blood was drained out of the patient and circulatory arrest instituted. The IVC was opened at the level of the renal vein and the cavotomy extended cephalad. The bloodless field provided excellent exposure of the thrombus which was adherent to the wall of the IVC just above the renal vein but not infiltrating it. It was dissected off bluntly at this level. The right atrium was explored by removing the atrial basket and the thrombus was released by blunt dissection through the atriotomy. The thrombus was gently delivered whole through the cavotomy in the abdomen. The thrombus measured approximately 20cm long (Figure 2).

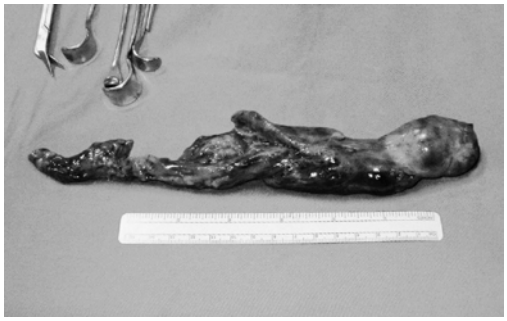

Figure 2*: Tumour thrombus retrieved from the inferior vena cava and right atrium*

The cavotomy was then closed using a non-absorbable vascular suture (Prolene 4/0). A schematic representation of the tumour thrombus extension, cavotomy and cannulation of the right atrium and ascending aorta for CPB is shown in Figure 3.

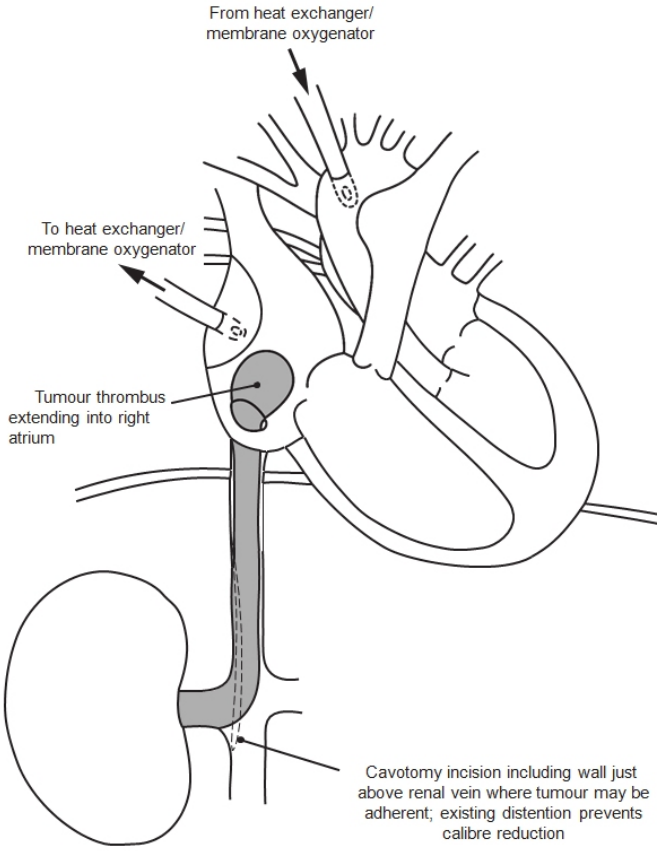

***Figure 3**: Diagram showing tumour thrombus extension, cavotomy and cannulation of the ascending aorta and right atrial appendage for cardio-pulmonary bypass*

Total circulatory arrest lasted 23 minutes, the circulation was restored and the patient slowly rewarmed. Cardiopulmonary bypass time was 157 minutes long. When the patient was fully rewarmed, CPB was terminated and protamine sulphate was given to reverse heparinisation. Post-operative bleeding from the adrenal bed complicated the surgery. This required re-laparatomy and packing of the area. The pack was removed two days later followed by uncomplicated recovery. Histology confirmed a Fuhrman nuclear grade IV clear cell carcinoma. Sections from the thrombus showed that it also consisted of tumour cells.

The patient remained disease-free for 15 months following surgery. He was then found to have local disease recurrence, though remaining asymptomatic.

Discussion

Venous extension of tumour thrombus is asymptomatic in 50 to 75% of cases because IVC obstruction is either incomplete or has occurred gradually, allowing collaterals to develop. When signs and symptoms are present they usually include lower limb oedema, distended superficial veins and a right-sided varicocele. Intra-atrial thrombus extension, as witnessed in this case, is also often asymptomatic.

Tumour thrombus usually consists of viable tumour cells extending out of the main renal tumour into the RV and IVC, though may sometimes be mixed with benign vascular thrombus. In the majority of cases this is adherent to the vascular endothelium or free-floating in the vein, and only rarely actually invades the endothelium.

Diagnosis is mainly radiological, with Ultrasound, CT, MRI and trans-oesophageal echocardiography (TOE) replacing venacavography. CT and MRI can both accurately define the upper extent of caval tumour while TOE is particularly useful when performed intra-operatively to monitor atrial thrombus and confirm its complete excision. All these modalities have their limitations particularly in diagnosing IVC wall invasion by tumour.

Accurate pre-operative staging is of paramount importance when planning surgery since the surgical approach will be determined by the cephalad extent of the tumour thrombus. Extension into the renal vein or proximal IVC can be safely managed by simple control of the IVC proximal and distal to the thrombus.[4] Involvement of the intrahepatic portion of the IVC often requires more complex manoeuvres such as mobilisation of the right lobe of the liver to expose the retrohepatic and suprahepatic IVC. Pringle's manoeuvre to control hepatic inflow, ligation of the lumbar veins and control of the contralateral renal vein to prevent venous back bleeding may also be required.[5]

Excision of intra-atrial thrombus introduces greater technical difficulties. Simply cross clamping the IVC may compromise venous return with subsequent reduction in cardiac output, catastrophic hypotension and hypoperfusion of vital organs. It may also be associated with extensive haemorrhage from venous collaterals and hepatic venous congestion. These problems are overcome by performing the procedure under full cardio-pulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) allowing more control. CPB was employed with DHCA at 16^0C. Hypothermia protects vital organs during circulatory arrest. Previous data[6,7] have indicated that core body temperatures of 16 °C to 18 °C are safe for periods as long as 45 to 60 minutes, yet there is no satisfactory means to accurately monitor cerebral function during surgery. Stopping the circulation provides a bloodless operating field in which to open up the IVC, and right atrium if necessary, and remove the tumour thrombus completely under direct vision. Reported disadvantages of DHCA are a prolonged time on bypass since it takes around an hour each to cool the patient to 16^0C and to rewarm. There is also an increased risk of post-

operative bleeding, as witnessed by this case, due to full heparinisation while on CPB, despite administration of reversing agents. There is always the risk of hypoxic organ injury, especially cerebral.

This gentleman was disease-free 15 months after surgery but then developed local recurrence. In retrospect one might argue whether such major surgery should have been undertaken in the first place given the presence of such extensive disease. RCC is not radio or chemo-sensitive so surgical excision is the only hope of cure. Several reviews have shown that in the absence of metastasis, complete excision of tumour thrombus together with radical nephrectomy may be associated with up to 72% survival at 5 years.[8] Adverse prognostic factors for these patients are perinephric tumour extension and lymph node metastasis, which are similar to those in whom tumour thrombus is not present.

There are conflicting reports about the prognostic significance of the cephalad extent of tumour thrombus. A review of over one thousand patients demonstrated a statistically significant better overall survival in patients with thrombus in the RV compared to IVC involvemement.[9] Both were classified as pT3b tumours in previous TNM classifications. They have now been separated into different prognostic groups in the revised TNM classification.[10] Other reviewers have shown that intra-atrial thrombus is not associated with a reduced survival when compared to lower levels of thrombus extension.[11] On the other hand, invasion of the vascular endothelium by thrombus is associated with a poorer prognosis[12] and increased morbidity since resection and reconstruction of the IVC is necessary in such cases.

Besides attempting to improve survival and alleviate symptoms when present, surgery in these cases is also aimed at minimising potentially fatal complications of IVC and intra-atrial thrombus including pulmonary embolism, peripheral oedema and atrial arrhythmias. We feel that this, coupled with the possibility of a curative resection, justifies the decision to offer surgery after very thorough pre-operative counselling of the patient.

Conclusion

Surgery for tumour thrombus extension in RCC may be associated with a good prognosis if no distant metastases are identified and if the thrombus can be completely excised. The surgical approach will depend on the cephalad extension of the thrombus, hence the importance of accurate pre-operative staging. When intra-atrial extension is present, CPB together with DHCA is an option that guarantees an optimal bloodless field while protecting vital organs. This provides the best opportunity for complete surgical excision of intra-atrial tumour thrombus that is crucial in optimising patient prognosis.

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