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Metastatic duodenal carcinoma presenting as severe anaemia and extensive bilateral lower limb deep venous thrombosis

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Introduction

Small bowel malignancies are relatively uncommon, accounting for only 2% of all gastrointestinal malignancies (1). A population-based analysis revealed duodenum as the location of 55.7% of adenocarcinomas of the small intestine (2). Some of the known risk factors for duodenal adenocarcinoma (DA) include western diet, ingestion of alcohol, coffee and use of tobacco. However, the strength of these associations are small and at most times a causative agent is unidentified (2). Patients with familial adenomatous polyposis and Gardner syndrome also have been identified to have an increased risk of DA (2).

Diagnosis is often delayed, since symptoms do not occur until the tumour has grown to sufficient size or spread into distant sites. When symptoms do appear they are often nonspecific symptoms such as nausea, vomiting, vague abdominal pain, fatigue, weight loss etc. Advanced disease may present as symptomatic anaemia which could be secondary to iron deficiency anaemia and anaemia of chronic disease.

Malignancy is an identified risk factor for venous thromboembolism (VTE). Specific tumour characteristics coupled with patient's underlying comorbidities and factors related to treatment may lead to this devastating complication. The primary site of malignancy strongly influences on the risk of VTE. According to literature, the incidence of VTE is higher in patients with malignancies of the pancreas, stomach, brain, kidney, uterus, lung and ovary (3). Metastatic disease at the time of diagnosis is a strong predictor of VTE. Chew *et al.* (2008) analysing the incidence of VTE among patients with primary lung cancer reported that patients with adenocarcinoma developed VTE more often than those with squamous cell carcinoma (3). Although this may not be directly applicable to histological types of duodenal carcinomas, there may be a similar association. Literature on small bowel malignancies associated with VTE is scarce.

Surgical resection and palliative chemotherapy are management options in DA. Long term outcomes of DA are comparatively better than with other periampullary malignancies in patients who present at an early stage with resectable disease. Median survival of patients with metastatic disease is around 6 months (2).

Case presentation

Herein we report a 62-year-old female who presented with left sided painless lower limb swelling for five days, exertional shortness of breath and bilateral ankle swelling for two weeks, and constitutional symptoms for two months' duration. She was apparently well three months prior to the presentation. Since then she lost her appetite significantly and started to lose weight. Within the course of three months she lost nearly eight kilograms of weight. She complained of generalised malaise and fatigability and found it difficult to engage in her day-to-day activities.

Sooner she developed progressive worsening of shortness of breath. She noticed bilateral ankle swelling, without abdominal or facial swelling. She denied orthopnoea, paroxysmal nocturnal dyspnoea or passage of frothy urine. She had no symptoms suggestive of chronic liver cell disease. She had no overt bleeding manifestations. She denied any history of fever. She complained of abdominal discomfort and regurgitation after meals, but no recurrent episodes of vomiting. Her bowel habits were normal. She had no features suggestive of connective tissue diseases.

She was incidentally diagnosed to have a sphenoid wing meningioma five years ago when she was evaluated for a chronic headache. She had lost her clinic records and imaging details. According to the patient, as it was a small tumour, she was advised on conservative management. She had been asymptomatic since then without chronic headache, visual disturbances, limb weakness or numbness. She had menopause at the age of fifty years. She was a non-vegetarian and consumed an average Sri Lankan diet. There was no history of malignancies in her family.

On examination, she was an averagely built lady. She had marked pallor without icterus. She had no lymphadenopathy. There was right sided pitting ankle oedema and left-sided lower limb oedema extending up to knee without erythema or warmth. Other systemic examination including cardiovascular, respiratory, nervous system, abdominal and digital rectal examination were unremarkable.

Identified clinical problems were symptomatic anaemia and unilateral painless lower limb oedema in the background of constitutional symptoms. Our initial differential diagnoses were gastrointestinal (GI) malignancy, leukaemia, and essential thrombocythemia which could cause anaemia due to occult blood loss, marrow suppression and platelet dysfunction associated bleeding respectively. Deep venous thrombosis (DVT) was thought to be related to malignancy or hyperviscosity. Systemic lupus erythematosus or secondary antiphospholipid syndrome causing haemolytic anaemia and DVT were also considered.

Initial evaluation revealed severe anaemia with a haemoglobin value of 2.5 g/dL. Blood pictures repeatedly revealed features suggestive of iron deficiency anaemia (IDA) with morphologically normal other cell lines ruling out our differential diagnosis of leukaemia and myeloproliferative neoplasms. Serum ferritin was 15 µg/L. Stool for occult blood was twice positive. Thus we presumed this could be an occult bleeding from the gastrointestinal tract leading to IDA. Ultrasonography of abdomen disclosed a heterogeneous mass in the left lobe of the liver measuring 6.9 x 6.7 cm. Possible differential diagnoses were hepatoma or liver metastases. Although an upper GI endoscopy was planned, it was abandoned as the patient did not offer consent.

Meanwhile she was transfused with red cell concentrates (RCC) to optimize her haemoglobin level and started on oral iron therapy. Venous duplex scan of the left lower limb revealed deep venous thrombosis (DVT) involving left femoral, popliteal, and posterior tibial vessels. Upon further inquiry, we could not identify any precipitants like recent history of immobilization, trauma or use of hormonal replacement therapy. Thus we were left out with the possibility of a malignancy associated DVT. Except for ultrasonic features of a liver mass, neither the history nor the examination pointed towards any probable site of a malignancy. A contrast enhanced computed tomography (CECT) abdomen and pelvis was arranged. Meanwhile, a decision was made to anticoagulate her with subcutaneous low molecular weight heparin to prevent formation of thrombi and propagation of the existing clot, after weighing risk of bleeding from anticoagulation against the benefit of minimizing thrombosis and its consequences. By this time her haemoglobin was stable around 10 g/dL following transfusion of six packs of RCCs. Patient's CECT abdomen and pelvis revealed a malignant growth arising from first and second parts of the duodenum extending into pancreatic head and uncinate process with lung and liver metastases (Figure 1). There was DVT involving bilateral femoral, external iliac veins and right common iliac vein extending into inferior vena cava (IVC).

However, her haemoglobin level began to drop within the course of next few days probably secondary to disease process and due to anticoagulation. Considering the risk of bleeding

with long term anticoagulation, we proceeded with insertion of a permanent IVC filter (Figure 2). Patient was then transferred to the oncology unit for palliative care.

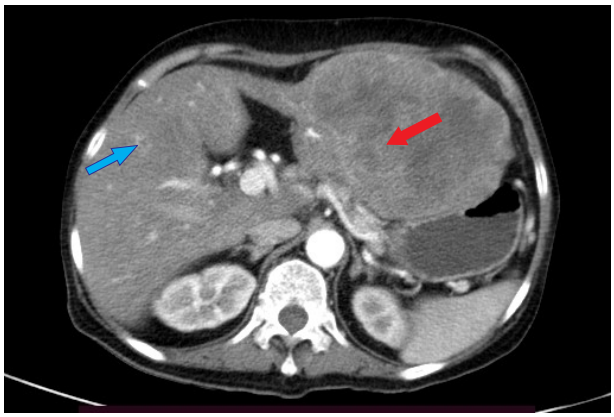

Figure 1: CT image of the mass lesion arising from duodenum (red arrow) with liver metastases (blue arrow)

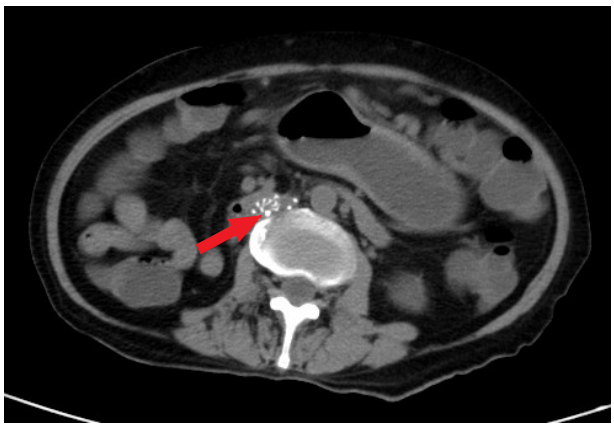

Figure 2: CT image of *in situ* inferior vena cava filter (red arrow)

Discussion

Small bowel malignancies are rare although the small bowel constitutes over 90% of the surface area of alimentary tract. Vague and nonspecific nature of symptoms makes early diagnosis of small bowel malignancies difficult. Common symptoms are abdominal discomfort, nausea, vomiting and weight loss. In advanced disease, patients may present with symptoms of anaemia. Proximal small intestine being the major site of iron absorption, any malignancy involving this region would result in impaired iron absorption. Occult gastrointestinal blood loss due to malignant invasion also contributes to an iron deficiency anaemia (IDA). In fact, malignancy being a chronic disease may cause normochromic normocytic anaemia as well. This will give rise to a mixed population of hypochromic microcytic and normochromic normocytic red cells. Approximately one third of males and postmenopausal females presenting with IDA will eventually be diagnosed with an underlying pathology and GI malignancies are a common entity (4). In fact, 6 - 12% of patients with occult gastrointestinal bleeding are diagnosed with small bowel tumours (1). Therefore thorough evaluation of an unexplained iron deficiency anaemia is of utmost importance. Bidirectional GI endoscopy is the standard diagnostic modality in evaluation of the upper and lower GI tracts. In certain instances, radiological imaging can be used as an alternative (5).

Malignancy is an identified risk factor for venous thromboembolism, which is found in approximately 4 - 20% of individuals with malignancy (6). Overall, patients with malignancy constitute nearly one fifth of all patients with venous thromboembolism (6). The link between thrombosis and malignancy is multi-dementional. Malignancy *per se* leads to a hypercoagulable state as a consequence of release of inflammatory cytokines, activation of the clotting pathway, inhibition of natural anticoagulants, and impaired fibrinolysis. Presence of other comorbidities, disease status, and therapeutic interventions, may also contribute to the occurrence of venous thromboembolism (VTE). Anticoagulation serves as the mainstay of treatment for VTE in individuals with malignancy. The optimal duration of treatment is indefinite, but current recommendation states at least 6 months of treatment for thrombosis associated with cancer and longer if the patient has active cancer or is actively receiving anti-neoplastic treatment (6). Associated risk of bleeding with oral anticoagulants may prohibit its use in some patients. In such context inferior vena cava (IVC) filters come into play. Placement of an IVC filter to prevent pulmonary embolism itself is not without risk. Therefore, indications should be carefully validated. In our patient, drop in haemoglobin despite repeated transfusions was an indication to proceed

with IVC filter placement. Landmark studies PREPIC (Interruption of Inferior Vena Cava by a Retrievable Filter for the Prevention of Recurrent Pulmonary Embolism: a randomised, open label study) and PREPIC 2 have revealed that IVC filters confer no clinical benefit in patients who are candidates for anticoagulation (7).

Conclusions

This case illustrates that atypical presentations of rare malignancies pose a significant challenge in diagnosis. Unexplained IDA should always be thoroughly evaluated. Lower limb DVT could be the first presentation of a malignancy.

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