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Multiple Myeloma Presenting in Unusual Extramedullary Sites in a 62 Year Old Female from Kigali, Rwanda: Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EA and LKT designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors PN, KT, JI and JJN managed the analyses of the study. Authors PK, IN and TN managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Multiple myeloma (MM) is a malignant hematological tumor that mainly manifests as osseous lesions in the bone marrow and skeletal bones. It rarely presents in extramedullary sites. Patients with extramedullary disease have been noted to have advanced stage disease with poor prognosis. We describe the clinical, radiological and pathological manifestations of a 62 year old Rwandan female who presented with extramedullary plasmacytoma involving multiple sites including the pleura, pancreas and gall bladder.

Case Presentation: A 62 year old Rwandan female presented with a three week history of intractable post-prandial vomiting, nausea, progressive weight loss, generalized body pain and limb weakness. Our diagnostic work-up showed soft tissue tumors involving multiple organs particularly pleura, pancreas and gall bladder along with diffuse lytic bone lesions in the ribs, spine and pelvis. Laboratory tests showed increased serum amylase, lipase, calcium, lactate dehydrogenase and CA125. Histopathology of the core biopsy of the pleura showed infiltration of monotonous atypical plasma cells. A diagnosis of MM with multiple extramedullary lesions was made. The patient initially improved and reached a partial response on bortezomib, dexamethasone and lenalidomide. However, five months after the initial diagnosis, she died from complications of the disease.

Conclusion: MM may be challenging to diagnose when it presents in unusual sites as extramedullary plasmacytomas.

Keywords: Multiple myeloma; extramedullary plasmacytoma; Rwanda.

1. INTRODUCTION

Multiple myeloma (MM) is a malignant clonal proliferation of plasma cells that produce a monoclonal protein [1]. In MM, the bone marrow and skeletal system are the most common sites of disease involvement. MM is the most common primary malignant tumor of bone and affects approximately 40% of patients [2]. MM is a disease of older adults with a median age of 66 years. Only 10% of patients have been found to be younger than 50 years and only 2% less than 40 years. MM manifests as three major categories: diffuse bone disease (myelomatosis); solitary plasmacytoma of bone or as extramedullary (extraosseous) plasmacytoma (EMP). EMP mainly involves, the kidney, spleen and the liver [3].

MM involving extramedullary sites (pleura, pancreas and bile duct) are indeed a rare occurrence [4-6]. The patient's clinical and laboratory findings are usually very non-specific and definitive diagnosis depends on histopathological analysis. Malignant myelomatous pleural effusions are even more unusual, occurring in less than 1% of cases of multiple myeloma.

Kintzer et al. 1978 reported that the incidence of pleural effusions in patients with multiple myeloma was only 6%. The pathogenesis of myelomatous pleural effusions may be due to direct extension or infiltration of tumor deposits on pleura or lymphatic obstruction from mediastinal lymph node infiltration. They are most commonly seen in patients with IgA myeloma, followed by lambda chain myeloma and IgG myeloma [2].

Other authors have described myelomatous lesions in the pancreas and gall bladder, other rare sites for MM. The involvement of the gall bladder has only been described in a handful of cases and that of the pancreas in less than 30 cases [7].

We describe the clinical, radiological and pathological features of a 62 years old female who presented to our hospital with MM and extramedullary manifestation involving the pleura, pancreas, retroperitoneum and gall bladder.

2. CASE PRESENTATION

A 62 year old female Rwandan presented to our hospital with a three weeks history of intractable late (1-hour) post-prandial vomiting, nausea, progressive weight loss, generalized body pain and limb weakness. She reported having lost 6-kg in the previous two months. However, she had no fever, hematemesis or melena, but mild peri-umbilical pain and constipation. She was para two and had menopause at 48. No other significant medical history was reported. There was no family history or a history of exposure to radiation.

On physical examination, she appeared very weak and dehydrated. Her temperature was 36.5°C. Her blood pressure was 130/85 mmHg, she had a regular tachycardia with a pulse rate 104 beats per minute, respiratory rate 16 breathes per minute, as well as an oxygen saturation of 96% while breathing ambient air. She weighed 90 kg. She was not pale or jaundiced and had no palpable peripheral lymphadenopathy, skin rash, joint swelling, tenderness nor deformity. On systemic examination, she had reduced breath sounds on examination of her lung bases, the abdomen was mildly distended, without significant organomegaly. Other systems had unremarkable findings.

Laboratory investigations (detailed in the Table 1 below) showed no definitive M-spike on serum protein electrophoresis, tests for Ig A were not done. Serum free light chain (SFLC) showed lambda light chain disease. There were also increased levels of serum amylase, lipase, calcium, lactate dehydrogenase (LDH), and creatinine.

Bone marrow aspiration showed that 70% of the cells had plasmacytoid morphology and biopsy showed features of a plasma cell neoplasm.

Contrasted CT scan of the abdomen showed retroperitoneal and paravertebral mass lesions, homogeneous enlargement of the pancreas with peripancreatic fluid collection and fat stranding, acute acalculous cholecystitis, bilateral small pleural effusions, ascites and diffuse lytic bone lesions involving ribs, spine and pelvis.

The patient was initially treated with intravenous fluids, ondansentron and acetaminophen.

Further investigations were carried out to confirm the diagnosis. The patient was referred to another hospital in India for further diagnostic workup and treatment.

An initial PET-CT scan confirmed the presence of large metabolically active soft tissue density masses involving the pancreas, gall bladder, periportal, retroperitoneal, mediastinal, paravertebral, left renal hilar regions,

Table 1. Results of laboratory investigations

Laboratory test	Result	Normal range
Haemoglobin	**11.7**g/dL	12-18 g/dL
ESR	70 mm / hr	
WBC (total)	7.2 x 10^9 / L	4-11 x 10^9 / L
Platelets	163 x 10^9 / L	150-400 x 10^9 / L
Urea	7.0 µmol/L	2.5-7.5 µmol/L
Serum creatinine	**123 µmol/L**	44-106 µmol/L
C-reactive protein	**5.9 mg/dL**	<0.6 mg/dL
Serum amylase	**212 IU/L**	25-125 IU/L
Serum lipase	**186 IU/L**	7-60 IU/L
Serum total calcium	**3.12 mmol/L**	2.2-2.6 mmol/L
Serum globulin	**1.9 g/dL**	2.0-3.5 g/Dl
Blood glucose	4.2 mmol/L	
Tumor markers		
CA 125	**65.8µ/ml**	0.1-30 µ/ml
CA 19.9	26.4 µ/ml	<35 µ/ml
CEA	0.74 ng/ml	0-5 ng/ml
Liver function tests		
Total protein	62 g/L	60-80 g/L
Serum albumin	33 g/L	36-50 g/L
Lactate dehydrogenase	**758 iu/L**	135-225 iu/L
Aspartate transferase	**58 iu/L**	<50 iu/L
Alanine transferase	**54 iu/L**	<50 iu/L
Serum free lambda levels	**21.4 mg/dL**	
Serum free Kappa levels	**1.5 mg/dL**	
Kappa: lambda ratio	**0.070**	0.26-1.65
Bilirubin		
Total	12.8 µmol/L	12-24 µmol/L
Differential	3.5 µmol/L	0-7 µmol/L

Abnormal results are highlighted in bold.

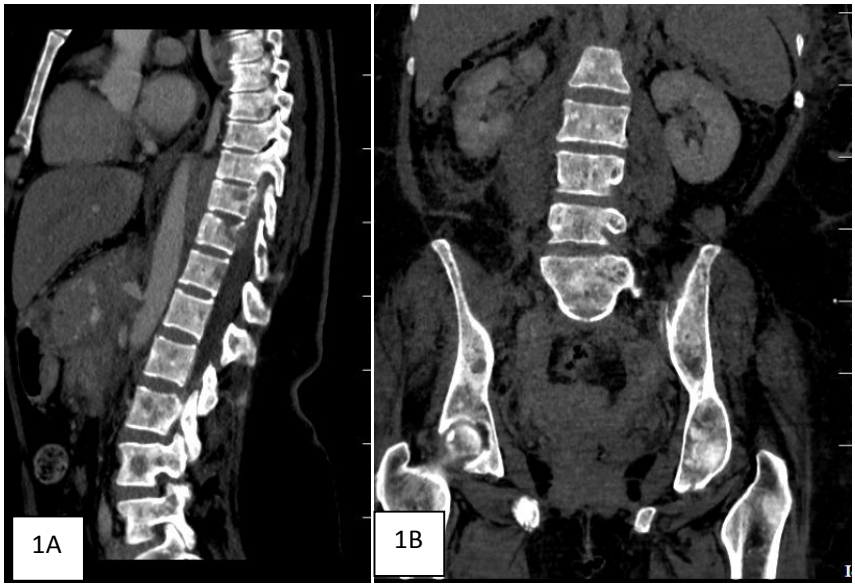

Fig. 1. Showing (A & B) "punched out" lesions in the vertebral bodies and pelvic bones

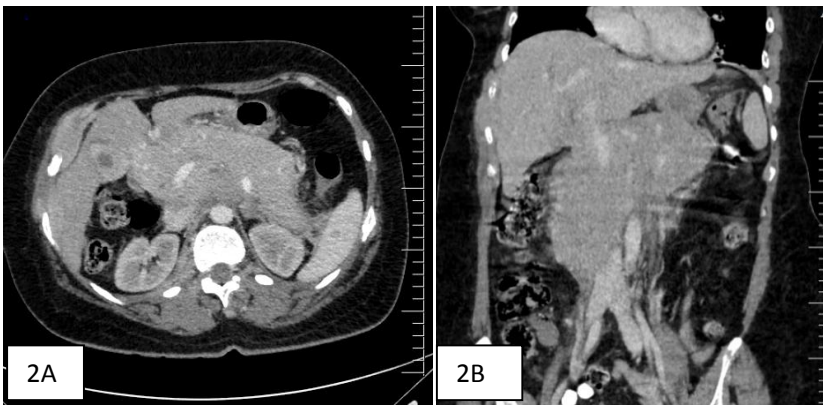

Fig. 2. Showing (A) extra medullary manifestation with infiltration of the pancreas and gall bladder (before treatment) (B) Infiltration of the common bile duct and porta hepatis (before treatment)

pleura and extrapleural masses, right inguinal lymphnode and left infrahilar region, inferior to the left atrium and thyroid nodules.

Pleural fluid aspiration, core biopsy of the pleura and ultrasound guided biopsy of the pre hepatic mass were done. Cytology of pleural fluid showed acellular material that was bloody and not diagnostic. Histopathological analysis of the core biopsies of both the pleura and perihepatic masses showed infiltration by a population of monotonous neoplastic plasma cells with characteristic eccentrically placed nuclei, abundant cytoplasm and occasional binucleate cells infiltrating the surrounding muscle in sheets.

A diagnosis of MM with extramedullary involvement of the pleura, pancreas and gall bladder was made.

The diagnosis of MM was confirmed using immunohistochemistry; the neoplastic cells where positive for CD138, MUM-1 and lambda light chain and negative for CD3, CD20, CD45, kappa light chain and pancytokeratin. Due to limited resources, we were unable to undertake chromosomal studies to determine the associated chromosomal abnormalities.

The diagnosis was MM with multiple organ extramedullary involvement. She was managed with a palliative chemotherapy

regimen of bortezomib, dexamethasone and lenalidomide.

On returning from India, subsequent imaging showed improvement with resolution of some soft tissue lesions in pleura and abdomen. However, she later developed a chest infection and a repeat chest CT scan showed pleural thickening confirmed as relapsed pleural MM on histopathology.

The chest infection was successfully treated with intravenous antibiotics and supportive care. The patient was discharged from hospital with a plan to continue chemotherapy on an outpatient basis, but she was re-admitted only a week later with symptoms of gastrointestinal upset and respiratory distress. She was diagnosed with severe chest infection complicated by Acute Respiratory Distress Syndrome and respiratory failure, which led to death.

3. DISCUSSION

MM rarely manifests in extra medullary locations and when it does it is even more rarely seen in the pleura, pancreas, retroperitoneum and gall bladder [4]. It has also been observed that the majority of patients with pleural effusions in MM have non myelomatous pleural effusions [8,9].

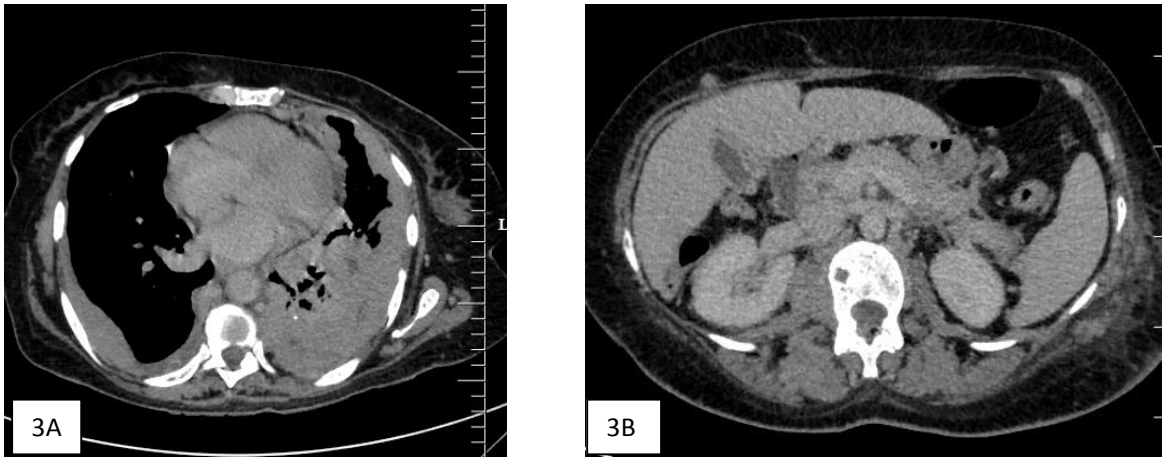

Fig. 3. Showing (A) pleural based masses and (B) showing resorption of pancreatic and gall bladder lesions after chemotherapy

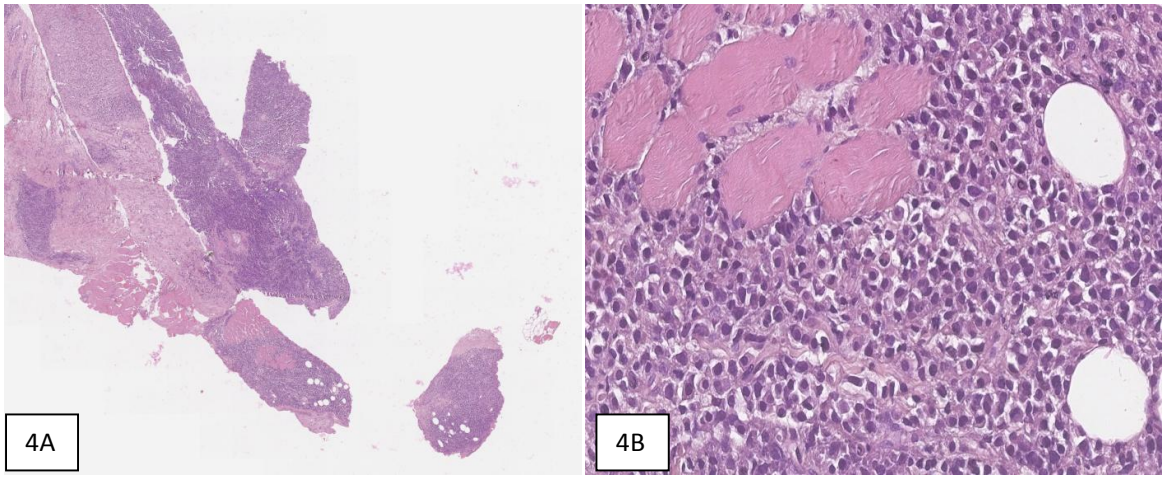

Fig. 4. Showing (A) pleura biopsy cores, the dark blue areas are infiltrated with malignant plasma cells and the surrounding muscle and fat is involved as well (magnification X 50) and (B) showing malignant plasma cells and some binucleated cells infiltrating the pleura and the surrounding muscle in sheets(magnification X 400)

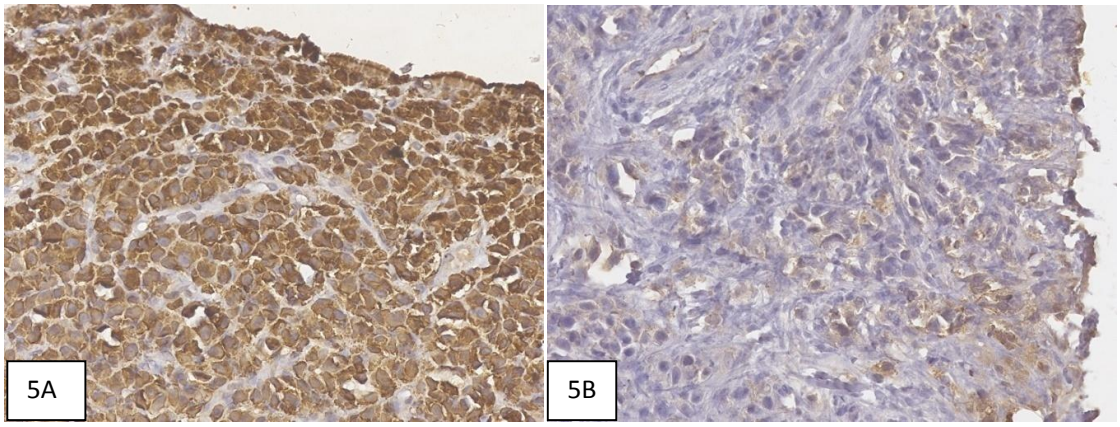

Fig. 5. Showing (A) strong positivity for lambda light chain and (B) negative staining for Kappa light chain

EMP involving the pleura causes pleural thickening and effusion. Colonna et al 2010 described two patients who had marked diffuse pleural thickening that mimicked mesothelioma [10]. The diagnosis is therefore best confirmed by histopathological examination of pleural biopsy or cytological analysis together with flow cytometry of the pleural effusion [2]. Our patient was admitted for shortness of breath and cough. The radiological findings of an effusion and pleural thickening led to the investigation for the cause of these features. Histopathology and immunohistochemistry confirmed the diagnosis of MM. Definitive diagnosis for pleural involvement by MM involves the confirmation using immunohistochemistry markers. Babu et al, 2017 have reported that pleural involvement by PCM carries a poor prognosis with survival of only up to four months [11].

Our patient also had abdominal disease in addition to the multiple osteolytic radiological lesions of MM. This presentation is rather atypical but has been documented in a few MM patients with EMP involving the chest and abdomen [12]. Coss et al. [13] described a case of MM with pancreatic head involvement and subsequent biliary tract involvement. Our patient had homogeneous enlargement of the pancreas with peripancreatic fluid collection and fat stranding, as well as features of acute acalculous cholecystitis. These radiological features confirmed by histopathological examination subsided with definitive chemotherapy treatment of MM. Studies have shown that involvement of the pancreas as EMP is extremely rare [7, 14].

The gall bladder involvement in our patient mimicked an acute cholecystitis. Less than ten cases have been reported in the literature. These tumors may also manifest as biliary obstruction or may be asymptomatic, making diagnosis difficult. In some instances detected during imaging for other disease conditions [15,16].

In the early stages, like in our patient, the gall bladder lesions present as acute cholecystitis, whereas in advanced disease they can directly invade liver and biliary tract, causing biliary obstruction, and lymph nodal or distant metastases [17]. The biliary as well as the pancreatic lesions resolved on repeat CT scan after definitive chemotherapy.

An interesting feature of our case was the elevation of CA125 levels. This tumor marker, also known as carbohydrate antigen 125, is observed in several malignancies, most notably ovarian carcinoma. The production of CA125 by MM cells is exceedingly rare. Only a few case reports have described this phenomenon in MM [18,19]. In regard to the pathogenesis of myeloma and CA125, it has been observed in other hematological malignancies that the malignant cells secrete interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) these are thought to stimulate mesothelial cells to secrete CA125[20], and indeed our patient had disease involvement of the pleura, pancreas and gall bladder.

SPEP studies showed no definitive M-spike. Some authors have shown that only 20% of patients with EMP have a small M-protein, which is most commonly IgA [21]. SFLC showed lambda light chain disease. Our patient belongs

to the category of patients with lambda chain disease, previously known as “Bence-Jones myeloma”. About one in five MM patients produce only light chains and patients with lambda light chain disease have a three times worse prognosis than those with kappa light chain [22].

Our patient also had hyperamylasaemia and presented with symptoms like those of acute pancreatitis which included nausea, vomiting, loss of appetite and weight loss. Ross et al. 2002 found no pancreatic pathology in a 42-year-old woman who presented with hyperamylasaemia. This patient and others with hyperamylasaemia have been noted to have extensive extramedullary disease with a high tumor burden and poor prognosis [23]. Such patients also have very poor treatment response with frequent relapses and hence overall poor outcomes. Raised amylase in non epithelial cancers like MM carries a poor prognosis, however it is yet unknown how the myeloma cells exactly contribute to the raised serum amylase levels [24].

Our patient had multiple poor prognostic markers which included: osseous pathology and multiple sites of extramedullary disease including the pleura, lambda light chain disease, hyperamylasaemia elevated lactate dehydrogenase, and extensive bone marrow infiltration. She gradually deteriorated and succumbed to her illness in a few months. This is comparable to what other authors have found: patients with MM and extramedullary disease have advanced stage disease and a very poor prognosis, with a median survival of less than six months [25].

4. CONCLUSION

MM may be challenging to diagnose when it presents in unusual sites as extramedullary plasmacytomas. However, it must be suspected in all patients who have concurrent osteolytic lesions, especially when they are in their 5th or 6th decade of life**.** We present the first case from Africa of an unusual case of MM that involved three rare extramedullary sites: pleura, pancreas and gall bladder.

CONSENT AND ETHICAL APPROVAL

Ethical approval was obtained for the Institutional Review board of OSHEN- King Faisal Hospital, Kigali, Rwanda. Written informed consent was obtained from the patient's next-of-kin for publication of this case report and any accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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