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ACUTE ON CHRONIC LIVER FAILURE SECONDARY TO METASTATIC ADENOCARCINOMA OF THE BONE MARROW WITH UNKNOWN PRIMARY

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ABSTRACT
Metastatic adenocarcinoma from solid organs, to the bone marrow is a catastrophic, but rare disease entity. Primary tumours most commonly originate in the lung, breast, thyroid or prostate. In many patients, the primary remains unknown. Most patients present with features of bone marrow failure and recurrent infections and in most cases, fatality is inevitable. Here we present a patient who was diagnosed eventually as poorly differentiated metastatic bone marrow adenocarcinosis, whose index presentation was that of acute on chronic liver failure; a presentation that has never been reported before.

INTRODUCTION

Bone marrow metastases seen with solid tumours are quite uncommon. Malignancies of prostate, lung, thyroid, stomach and breast are most commonly implicated in this situation. Bone marrow metastases in solid tumours are a harbinger of poor prognosis. Presentations mostly include those of severe anemia and bleeding diathesis due to bone marrow failure or fulminant infections. Acute on chronic liver failure (ACLF) as a presentation of bone marrow carcinosis has never been reported before. Common precipitants of acute or chronic liver failure include spontaneous bacterial peritonitis, hepatocellular carcinoma, portal vein thrombosis, acute viral infections, reactivation of chronic viral hepatitis and surgical procedures. Here we present the case of a middle aged woman who had features of acute on chronic liver failure and in whom the acute event was possibly extensive bone marrow carcinosis from an unknown primary.

CASE REPORT

A 44 year old housewife, known case of hypothyroidism since 10 years, well controlled on thryoxine replacement and without other co morbidities presented to our emergency room with a one month history of painless progressive non cholestatic jaundice and anorexia without associated prodrome. This was followed by painless abdominal distension since a period of 2 weeks with bilateral leg swelling. There was no history of facial swelling or decreased urine output. The patient's husband stated that she had developed spontaneous bruises over her right neck and lower abdomen within the past few days. The patient subsequently developed altered sensorium in a period of two days associated with irrelevant talk and excessive drowsiness. Her family denied prior jaundice, blood transfusions, alternative medicine intake, trauma, surgeries or abortions. There was no history suggestive of bone pains, loss of weight, or fever with drenching sweats, convulsions and fatigability. The husband had noted that the patient suffered from intermittent 'twisting and abnormal spastic movements' at the hand, unilaterally since one week. At admission, the patient had poor alertness and was talking irrelevantly. Her blood pressure

was 122/68 mm of Hg in the right upper brachial region, pulse rate 108 per minute and respiratory rate 26 per minute. She was moderately built with central obesity. The neck was supple to palpation and without nodularity; a localized area of ecchymosis was evident on the right side of the neck with supraclavicular extension. Pallor and icterus was present in the absence of clubbing, cyanosis and peripheral adenopathy. Abdominal examination revealed firm hepatosplenomegaly with grade II ascites and a large 6 x 7 centimetres ecchymotic patch over the right lower quadrant of the abdomen. A provisional diagnosis of ACLF was made; the acute event suspected to be viral hepatitis and the chronic liver disease etiology secondary to non alcoholic fatty liver disease, considering the presence of hypothyroidism and metabolic profile of the patient. Relevant laboratory investigations are shown in Table 1. Further results of blood investigations revealed serum lactate dehydrogenase of 5847 IU/L (normal 265 to 500), hypomagnesemia, hypophophatemia, low normal parathormone in the presence of very high levels of serum ferritin (2200 microgram/L, normal 10 to 150) with a preserved serum iron, total iron binding capacity and a high transferrin saturation. In the meantime, acute viral markers (hepatitis A, hepatitis E, Ebstein-Barr virus, Cytomegalovirus and Parvovirus B19) were found to be negative, malaria antigen and leptospira IgM hepatitis B and C viral study were non reactive, including DNA and RNA studies respectively. Autoimmune markers (antinuclear antibody, anti mitochondrial antibody, anti LKM antibody, anti liver soluble antigen, anti smooth muscle antibody) were negative. The tumor markers, alfa feto protein, CA 19-9 and beta-human chorionic gonadotropin were within normal limits. Serum fibrinogen was very low with a normal lipid profile. The patient underwent imaging of the abdomen which revealed a heterogeneously enhancing hepatic parenchyma with periportal edema and mildly irregular hepatic outlines consistent with liver parenchymal disease. In addition, features of portal hypertension (prominent portal vein, multiple abdominal collaterals and moderate ascites) were also noted. Chest imaging revealed multifocal sclerotic lesions involving the axial skeleton (mostly thoraco-lumbar spine, showing coarse osseous trabeculae with multiple subcentimeter sized sclerotic lesions of varying sizes) which was suspicious for marrow infiltrative disorder (Figure 1). In view of rapidly developing cytopenias in presence of bony lesions, a bone marrow aspiration and biopsy was done revealing dry tap. Hence an imprint of the bone marrow biopsy was done to study cellularity that showed presence of few large bizzare, pleomorphic cells seen with enlarged, hyperchromatic, pleomorphic, irregular nuclei with high N:C ratio, prominent eosinophilic nucleoli and abundant cytoplasm, features suggestive of malignant cell infiltration. Bone marrow biopsy showed presence of tumor infiltration in small aggregates, clusters and single cell infiltration with abundant background fibrosis and myxoid material. The tumor cells had enlarged, hyperchromatic, pleomorphic nuclei with high N:C ratio, irregular nuclear membrane, coarse chromatin, prominent nucleoli and abundant vacuolated cytoplasm. Were PANCK+, CD45-, CD3-, CD20-, and CD30-. Normal bone marrow components were diminished. Immunohistochemistry for synaptophysin, chromogranin and calcitonin were also negative. These features were suggestive of metastatic bone marrow infiltration by poorly differentiated adenocarcinoma with secondary myelofibrosis (Figure 2), with patient developing signs and symptoms of progressive liver failure, leading to disseminated intravascular coagulation (DIC). The patient's condition rapidly worsened with further spontaneous bleeding events and multi organ failure. She was provided aggressive management in the form of broad spectrum antimicrobial cover (Meropenem 1g, 8 hourly + Teichoplanin 400mg 24 hourly + Anidulafungin 100mg, followed by 50mg 24 hourly), nutritional supplementation (2Kcal/mL enteral nutrition through nasogastric tube feeds), human albumin infusions (20 to 40 g per day), blood and blood products transfusions based on thromboelastographic analysis. Progression was relentless and cardiorespiratory arrest requiring mechanical ventilation and a rising need for inotropic support to maintain hemodynamics intervened. She eventually died on the fourth day of hospital stay. At death, a final diagnosis of acute on chronic liver failure, the acute insult being metastatic adenocarcinosis to bone marrow of unknown primary with resultant hypocalcemia, hypomagnesemia, hyperphosphatemia, DIC, multiorgan failure and refractory shock was made.

Table 1. Investigations at admission and on day one and day three of hospital stays

Parameter	Normal	Day 0	Day 1	Day 3
Hemoglobin (g/dL)	12 to 15	10.2	5.5	6.2
Total leucocyte count (x 109/L)	4 to 11	9.1	4.2	1.3
Platelet count (x 10^9/L)	150 to400	50	35	28
Total bilirubin (mg/dL)	0.3 to 1.2	8.8	12.3	18.6
Direct bilirubin (mg/dL)	0.2	5.2	8.4	11.6
Aspartate transaminase (AST, IU/L)	5 to 40	418	556	680
Alanine transaminase (ALT, IU/L)	7 to 35	73	88	100
Alkaline phosphatise (SAP, IU/L)	32 to 92	1114	1221	1348
Gamma glutamyl transpeptidase (GGT, IU/L)	7 to 64	184	188	212
Albumin (g/dL)	3.5 to 5.2	1.7	2.2	2.3
Calcium(corrected, mg/dL)	8.4 To 10.2	4.2	5.6	8.2

Figure 1. Computed tomography of the abdomen showing features of chronic liver disease with portal hypertension in the form of tongue shaped left lobe hypertrophy and caudate lobe enlargement (red arrows); presence of collaterals (yellow arrows) in the presence of multiple lytic bone lesions (blue arrow)

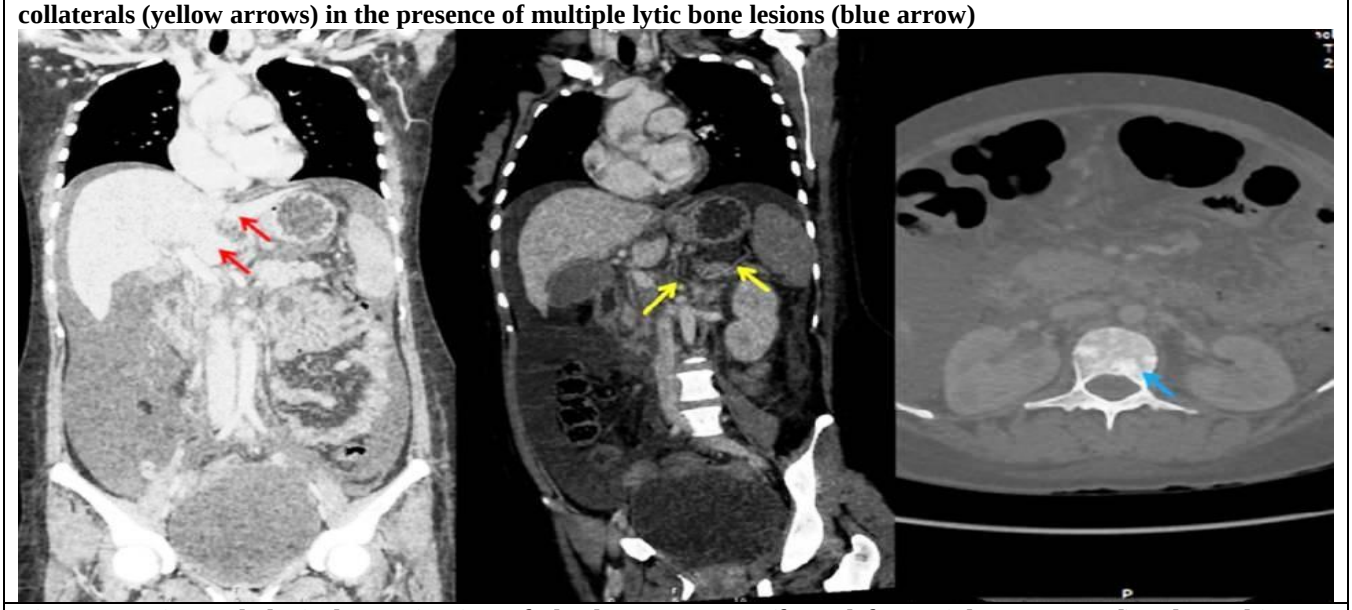
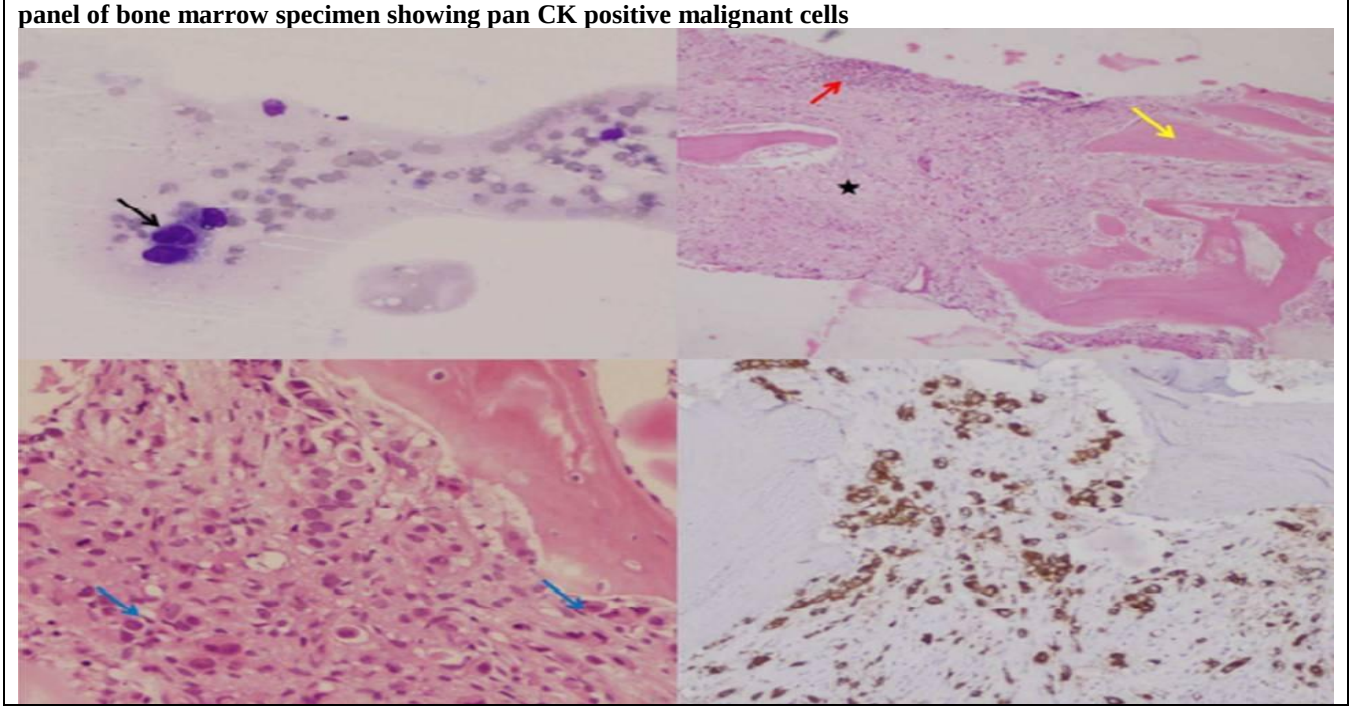


Figure 2. Histopathological examination of the bone marrow (from left to right; top panel) - large bizzare, pleomorphic cells seen with enlarged, hyperchromatic, irregular nuclei with high N:C ratio (Giemsa stain, 40X; black arrow); scanner view of bone marrow histology showing bony trabeculae (yellow arrow) with small areas of normocellularity (red arrow) and extensive areas of secondary myleofibrosis (star); (from left to right, bottom panel) - bone marrow histopathology revealing presence of tumor infiltration in small aggregates , clusters and single cell infiltration with abundant background fibrosis and myxoid material. The tumor cells have enlarged, hyperchromatic, pleomorphic nuclei with high N:C ratio, irregular nuclear membrane, coarse chromatin, prominent nucleoli and abundant vacuolated cytoplasm (blue arrows; H&E stain, 100X); Immunohistochemistry panel of bone marrow specimen showing pan CK positive malignant cells



DISCUSSION AND CONCLUSION

Metastatic adenocarcinoma to the bone marrow is a rare phenomenon with solid tumors. Crivellari and co-workers in 1995 reported a case of extensive malignant bone marrow infiltration in a 65 year old man with severe symptomatic anemia. Histopathology revealed diffuse

paratrabecular infiltration of poorly differentiated adenocarcinoma of gastric origin. A chemotherapy regimen followed by resection of the primary was done with the patient having clinical remission 27 months on follow up [1]. Mathew and colleagues reported a case of skeletal and bone marrow infiltration by squamous cell carcinoma of the buccal cavity in patient who presented with bone pains and severe anemia, a scenario which is quite rare considering the fact that distant metastases with head and neck cancers seldom occurs [2]. Mizuno and group reported the occurrence in bone marrow, in a 44 year old man, of mucinous moderately differentiated adecarcinoma which was the recurrence of a 11 year old treated gastric cancer, from the lymphoduct of the remnant stomach. The patient at presentation had severe anemia, a highly raised SAP and thrombocytopenia and developed a rapidly progressive course and developed haemolytic anemia and disseminated intravascular coagulation and subsequently died [3]. Koizumi et al reported the devastating occurrence of hemophagocytic syndrome in a patient of carcinoma prostate who had features of carcinomatous infiltration of the bone marrow [4]. In Salathiel and Wang's report, a 66 year old man presented with severe symptomatic anemia and thrombocytopenia with leucoerythroblastosis on peripheral smear and nodular lesions in the liver. He was later on diagnosed to have extensive neuroendocrine carcinomatous infiltration of the bone marrow and died after a rapidly progressive course. The primary tumor site was not identified [5]. In a series from Turkey, Ozkalemkas and co workers analyzed bone marrow aspirates and biopsies of 19 patients for diagnosis of the primary tumor on the basis of bone marrow carcinosis. They found out that anemia, thrombocytopenia, elevated red cell distribution width and hypoprotenemia were a classical tetrad in tumours of non haematological origin with dissemination into bone marrow. They concluded that presence of microangiopathic haemolytic anemia, leukoerythroblastosis on peripheral smear and unexplained cytopenias were strong indicators for bone marrow evaluation. In their series, primary was diagnosed in 10 patients (5 gastric, 3 prostate, 1 lung and 1 muscle) and no work up could disclose tumour origin in 5 patients (tumour of unknown origin, TUO). The survival of such patients, on an average range from few days to few weeks only [6]. Pleyer et al treated a patient of localized colorectal cancer in sepsis, with activated protein C after which the authors found that extensive bone marrow infiltration, of colorectal adenocarcinomatous cells occurred in the patient post treatment. Symptomatic bone marrow metastases secondary to colorectal adenocarcinoma is quite rare [7]. Jain et al, described the occurrence of bone marrow metastases, in malignant melanoma of unknown primary site. The organ of origin was confirmed on immunohistochemistry of bone marrow infiltrative malignant cells [8]. Metastatic transitional cell carcinoma of the bladder presenting as isolated anemia and thrombocytopenia secondary to bone marrow infiltration was reported in a patient by Fernandez and colleagues [9]. Proper immunohistochemistry helps in determining the primary tumour sites in patients of metastatic bone marrow disease with unknown primary site. This was shown by Wu and co workers in a series of 38 patients whoc underwent bone marrow evaluation for unexplained cytopenias and symptomatic anemia or bleeding diathesis. They found that most of the tumourous infiltration was of poorly differentiated adenocarcinoma type, with stomach being the most common site of origin [10]. List and co workers reported extensive adenocarcinomatous bone marrow carcinomatosis that led to disseminated intravascular coagulation in a patient who presented with bleeding diathesis [11]. In a series by Kaur et al, from Chandigarh, out of 784 bone marrow aspirations performed over 69 months, 9 patients revealed features of bone marrow metastases. The commonest symptom in these patients was fatigue and the commonest sign was pallor. Their patients had primary sites mainly that of stomach, followed by prostate, breast and lung. The authors state that normocytic normochromic anemia is commonly associated with bone marrow infiltration by malignant tumours. But the presence of a luekoerythroblastic blood picture, seen in about 35 to 50% of patients are of importance, as this is attributed to crowding out of marrow elements in presence of cytokine dysregulation and malignant infiltration. Dry or bloody marrow taps are also seen commonly with malignant bone marrow carcinosis, which is secondary to reactive myelofibrosis [12]. Selcukbiricik et al shed light on the importance of FDG-PET/CT scan in diagnosis of bone marrow metastases by solid organ tumours. In their cohort, 4 out of 10 patients had bone and bone marrow metastases whereas 6 patients had bone marrow involvement without bony lesions [13]. Pan et al reported a rare case of bronchial mucoepidermoid carcinoma of lung presenting with bleeding diathesis and severe anemia with generalized weakness and bone pains. Their patient also had a rapidly progressive course which culminated in death from multi organ haemorrhage secondary to disseminated intravascular coagulation [14]. Lesesve and Plenat in 2014 reported the occurrence of aggressive metastatic medullary carcinoma of thyroid in a patient who had bone marrow carcinosis. Their patient also presented with severe anemia and a rapidly fatal course [15].

In our case, the presentation was unlike reported in literature. Our patient had an ACLF presentation. The patient, who was a known hypothyroid on thyroxine supplementation, had imaging features suggestive of chronic liver disease and ascites analysis suggestive of portal hypertension. Acute events in ACLF are well defined and are at par with decompensation events in a known cirrhosis patient. These include sepsis such as spontaneous bacterial peritonitis or other infections, acute variceal bleeds, development of hepatocellular carcinoma, portal vein thrombosis or reactivation of chronic viral hepatitis. Apart from jaundice, ascites and encephalopathy, our patient also had symptomatic hypocalcaemia and

hyperferritinemia, high lactate dehydrogenase levels, hyperammonemia and evidence of severe coagulopathy. Metastatic diseases have not been identified as a precipitating event in ACLF. Metastatic poorly differentiated adenocarcinoma of the bone marrow is a rarity and its role as an acute event in ACLF has never being reported in literature. Apart from conventional precipitating events, extrahepatic metastatic diseases also must be kept in mind while caring for a patient of ACLF.

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