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Title: BONE MARROW NECROSIS: RARE PRESENTATION OF CHRONIC MYELOID NEOPLASMS SYSTEMIC REVIEW AND CASE REPORT

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Background:

The prevalence of bone marrow necrosis (BMN) with hematological malignancy (HM) is 0.3% to 2.2%. Very rarely, BMN has been reported with chronic myeloid neoplasms (CMN). BMN is defined as necrosis of myeloid tissue and medullary stroma in large areas of the hematopoietic bone marrow. The presence of BMN has also been associated with poor survival outcomes in HM.

Aims:

To describe the outcomes of CMN associated with BMN

Methods:

A literature search was conducted with MEDLINE. PubMED, and Google Scholar, using search terms bone marrow necrosis, myeloproliferative neoplasm, myeloid neoplasm, chronic myeloid neoplasms, polycythemia vera, essential thrombocythemia, and myelofibrosis. The search was limited to articles (ART) in English. Resulting in 21 ART. ART reporting about pediatric population and solely about acute leukemia were removed. A total of 7 publications comprising total of 8 cases spanning 29 years (1994-2023) were reviewed.

Results:

Our case is a 64M developed left hip pain with Hb: 94g/L, Plt: 30 $x10^9$/L, WBC: 6.1$x10^9$/L and peripheral blast (PB) 2%. After 3 non-diagnostic BmBx, there was suspicion for myeloproliferative neoplasm unclassifiable. Referral to Princess Margaret for diagnostic clarification. Repeat BmBx showed necrosis, granulopoiesis with left shift, with reticulin fibrosis grade 2, with blast >10%. Flow showed 14% of cells positive for CD13, CD33, CD34, CD45, CD71, CD105, CD117, CyMPO, HLA-DR and negative: sCD3, CyCD3, CD10, CD11b, CD14, CD16, CD19, CD35, CD36, CD56, CD64, cyCD79a, CD300e, TdT. Next Generation Sequencing (NGS): *ASXL1, DNMT3A, NPM1, TET2* with normal cytogenetics. Myeloid neoplasm with fibrosis accelerated phase. Patient was treated with induction chemotherapy and achieved remission.

Including our case, we found a total of 9 cases of BMN with a diagnosis of CMN (See table 1 for details). Patients experience bone pain in 66.7% of the cases (N=6/9), 55.6% (N=5/9) experience 1 or more constitutional symptoms of either fevers, drenching night sweats and/or unintentional weight loss. All (N=9/9, 100%) of the patients in this presentation experienced anemia and/or thrombocytopenia. One patient developed pancytopenia during hospitalization, repeat marrow BMN diagnosed concurrently with disease transformation to AML secondary to polycythemia vera. Three cases were lost to follow-up. Thirty-three percent (N=3/9) early mortality was seen, and one patient although time of death not provided, was transferred to a hospice. One patient with myeloid neoplasm and NPM1 and TET2 mutation responded well with induction and consolidation chemotherapy with resolution of BMN on repeat marrow. Our patient had undergone FLAG-IDA induction and achieved complete remission.

Summary/Conclusion:

BMN in CMN is a rare entity, patients often present with cytopenia. Bone pain and constitutional symptoms are the next most common clinical manifestations. BMN in this report also seems to be associated with poor prognostic outcomes. However, BMN poses diagnostic challenges, as the necrotized trephine provides little to no cellular component for diagnostic analysis; in such situations, NGS and cytogenetics have important diagnostic

implications, and may change the diagnosis from CMN to an acute leukemia, utilizing the ELN 2022 guidelines, which in turn has implications on treatment. In our case and Saito et al, in both cases although blast was below 10%, but the utilization of intensive chemotherapy resulted in positive patient outcomes.

Author	Patient demographics	Relevant clinical presentation	Important investigation results	Treatment	Outcomes
Majumdar et al., 1994	54M 5-year history of essential thrombocythemia confirmed by bone marrow biopsy treated with busulphan 4mg q2 weeks counts stable	1-week history of generalized pain, with more severe pain to ribs and back, decreased appetite, developed fevers, and night sweats Hb=103g/L Plt=144x10^9/L, WBC=5.6x10^9/L	1st BmBx – revealed BMN with no increase reticulin fibrosis Viral screening – negative 2nd BmBx due to persistent anemia Increased cellularity, and increase course reticulin staining Conclusion – patient developed post necrotic myelofibrosis	Bulsulphan treatment held patient	Not provided
Psydas et al., 2002 Case report of 20 patients, 2 were chronic MPNs	Case 1 43M MPN/MDS with reticulin fibrosis	Fatigue, anemia, and thrombopenia (details note provide in article)	BmBx – necrosis and moderate level of reticulin fibrosis	Not available	Not provided
	Case 2 41M CML with reticulin fibrosis	Bone pain and splenomegaly with anemia	BmBx – bone marrow necrosis, with mild reticulin fibrosis	Not available	Lost to follow-up after 1 month
Niscola et al., 2007	71M 15-year history of PV, treated with pipobroman followed by hydroxyurea but discontinued due to development of leg ulcers	5-day history of severe malaise, fevers, chills, dyspnea and appeared pale Spleen = 22cm Hb=90g/L, Plt=750x10^9/L, WBC=23x10^9/L	1st BmBx - dry tap, hypercellular marrow with 22% blast, AML 5 days after admission counts worsen Plt=9x10^9/L, WBC-0.5x10^9/L, and red blood cell transfusion dependent, and severe bone pain 2nd BmBx – massive BMN	Transfusion support	Death: 13-days after admission multiorgan failure
Choudhary et al., 2015	56F no prior medical history provided	15-day history of weakness, tiredness, fatigue, and fever Hb= 60g/L, PLt=40x10^9/L, WBC=5.4x10^9/L	BmBx- hemopoietic cells reduce, evidence of extensive bone marrow necrosis, and focal areas of mild myelofibrosis	Not available	Death: 5 days after admission
Shapiro et al., 2015	66F history of JAK2+ MPN-unclassifiable treated with hydroxyurea	3-week history of progressive back pain, fevers, drenching night sweats Hb=73g/L, plt=38x10^9/L, WBC=17x10^9/L	1st BmBx – fully necrotic sample 2nd BmBx – nondiagnostic necrotic sample • Flow cytometry – myeloblast population expressing CD34, CD117 • Marked lymphadenopathy in peritoneal and retroperitoneal cavities 3rd BmBx - nondiagnostic necrotic sample	Functional decline required ICU admission Chemotherapy doxorubicin and cytarabine initiated, but stopped after day 1.	Death: 3 weeks after initial hospital admission
Chambers et al., 2017	62F history of PV treatment with hydroxyures for past 4 years	Increasing weakness, confusion and fall leading to hospitalization Hb=73g/L, plt=46x10^9/L, WBC=6.1x10^9/L, elevated calcium levels	CT scan revealed lytic lesion in lateral aspect of T2, and small lytic lesion in the skull Multiple myeloma work-up negative 1st BmBx – extensive necrosis • Flow cytometry – EpCam, CD138, CD56 positive consistent with metastatic carcinoma • Repeat flow cytometry – increasing blast counts 2nd BmBx – transformation to AML	Transfusion support	Transfer to hospice unit Death – unknown
Saito et al., 2022	46M no past medical history provided	Presented with severe chest pain, and left hip pain impacting ability to walk Hb=136g/L, Plt=72x10^9/L, Wbc=2.6 x10^9/L, blast 1%	Cardiac work-up negative MRI showed diffuse signal alteration ^{18}F-fluorodeoxyglucse positron emission tomography scan - showed diffuse uptake in marrow, spleen, kidneys and muscle groups BmBx – complete bone marrow necrosis with Charcot-Leyden crystals, Molecular testing NPM1 and TET2	Due to rising Wbc 27x 10^9/L, with 8% blast and declining clinical status, patient treated as AML patient with induction chemotherapy with daunorubicin and cytosine arabinoside. Followed by consolidation chemotherapy. Patient was not candidate for allogenic stem cell transplant BmBx after 1st consolidation – complete resolution of bone marrow necrosis, and resolution of Charcot-Leyden crystals.	Completed consolidation treatment BmBx at 29months post-treatment confirmed remission and resolution of bone marrow necrosis and Charcot-Leyden crystals.
Our case	64M previously in good health	History of persistent shoulder pain, 8-10lbs unintentional weight loss over a few months Sought medical attention and bloodwork revealed: Hb = 94g/L, Plt = 30 x10^9/L, Wbc= 6.1x10^9/L and PB 2%. Required transfusion support	3 non-diagnostic BmBx 4th BmBx - suboptimal sample with necrosis noted, granulopoiesis shows left shift, with reticulin fibrosis grade 2, with blast >10%. Myeloid neoplasm in accelerated phase. NGS: ASXL1, DNMT3A, NPM1, TET2. Cyto: 46, XY [20]	Induction chemotherapy FLAG-IDA protocol	Remains in remission

Table 1 - Bone marrow necrosis in myeloid neoplasms

Keywords: Myelofibrosis, Bone Marrow Fibrosis, Myeloid malignancies, Osteonecrosis