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# Post-transplant relapse of therapy-related MDS as gastric myeloid sarcoma: Case report and review of literature

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ABSTRACT

*Introduction:* Myelodysplastic syndrome (MDS) are hematologic neoplasms characterized by morphologic dysplasia and ineffective hematopoiesis in the bone marrow. The only potentially curative therapy is stem cell transplant. However, relapse remains a major challenge and is seen in about 25–40% of cases. Myeloid sarcoma presenting as relapse post allogeneic transplant for myeloid neoplasms is rare. We report the sentinel case of a patient with MDS who relapsed as gastric myeloid sarcoma 1 ½ years after allogeneic stem cell transplant.
*Case Presentation:* Sixty-nine-year-old male who was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in 2006 and transitional cell bladder carcinoma in 2008. In 2011, he developed therapy-related myeloid neoplasm t(7;22) and no excess blasts. He was treated with Vidaza followed by a MUD hematopoietic stem cell transplant on 8/24/2012. In 2013 the patient developed anorexia and gastric biopsies showed severe gastritis. Repeat gastric biopsy on 02/05/2014 showed an extensive mononuclear infiltrate which could easily be confused with lymphocytes but staining showed myeloid sarcoma. Marrow was negative. The patient remained refractory to therapy and expired 08/10/2016.
*Conclusion:* In summary, we report the first case of GI relapse of MDS as a myeloid sarcoma post-transplant. We seek to alert our audience of this potentially serious diagnostic pitfall, particularly one that can be relatively easily resolved on the basis of immunohistochemical profiling.

## 1. Introduction

Myelodysplastic syndromes (MDS) are hematologic neoplasms characterized by morphologic dysplasia and ineffective hematopoiesis in the bone marrow. Various etiologies have been linked to MDS including previous chemotherapy exposure and radiation, as well as molecular aberrations such as gene mutations, abnormal gene expression, and genomic instability. MDS prognosis is assessed using the International Prognosis Scoring System (IPSS) and is determined by various factors, including chromosomal abnormalities [1]. MDS prognosis is generally poor, with a median overall survival ranging from a few months to 5 years with nearly 30% of patients eventually transforming to acute myeloid leukemia (AML) [2,3].

In some cases, treatment is aimed at managing patient cytopenias. Several pharmacologic agents are also available to target disease including azacitidine (Vidaza), a hypomethylating agent, as well as lenalidomide, a thalidomide analog for patients with the 5q deletion syndrome [4]. Allogeneic stem cell transplantation (SCT) has been shown to be the only treatment with curative potential and is recommended for MDS patients with intermediate-2 and high-risk disease, as well as in those with therapy-related MDS [5,6]. MDS is currently the third most common indication for SCT [6].

Relapse remains a major challenge and is seen in about 25–40% of transplanted patients and is also the major cause of mortality in SCT patients [6]. Post-transplant relapse is associated with low 3-year survival rate and currently has no available standard of care [7].

Myeloid sarcoma, also known as granulocytic sarcoma or chloroma, is used to refer to extra-medullary manifestation of AML. It can occur de novo, before, or post treatment of AML, myeloproliferative neoplasm (MPN), or MDS and may also present as relapsed disease after SCT [8]. Myeloid sarcoma presenting as relapse post allogeneic transplant for myeloid neoplasms is rare and commonly misdiagnosed, potentially

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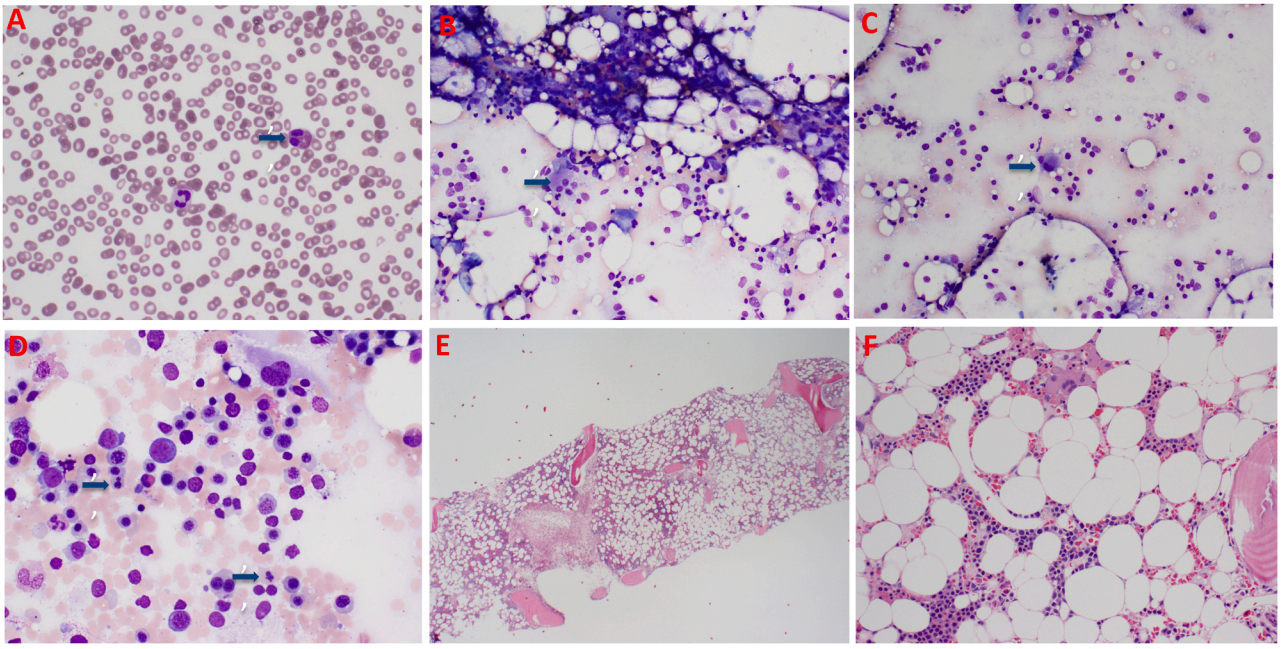


**Fig. 1.** Bone marrow biopsy before allogeneic SCT, showing low grade MDS with trilineage dysplasia and no obvious increase in blasts. A. Peripheral blood: Pseudo-Pelger-Huet neutrophils with hypogranular cytoplasm and hypolobated nuclei. B and C. Dysplastic megakaryocytes with nuclear hypolobation and nuclear separation. D. Dysplastic erythroid precursors with nuclear irregularity or budding. E and F. Normocellular bone marrow with relative erythroid hyperplasia, dysplastic megakaryocytes, and no obvious increase in blasts.

leading to incorrect or delayed treatment [8]. When relapse does occur as myeloid sarcoma in the post-transplant setting it is mostly in patients with a pre-transplant diagnosis of AML [8–12]. The incidence of MDS patients relapsing as myeloid sarcoma is exceedingly rare and has only very rarely been reported. There currently exist only two case reports to the best of our knowledge thus far in this regard [13,14]. None of these record involvement of the gastrointestinal tract. We hereby report a patient with MDS who relapsed as gastric myeloid sarcoma one and a half years after allogeneic SCT.

## 2. Case presentation

The patient is a 69-year-old male who was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in 2006. Cytogenetic studies showed 13q deletion. After multiple chemotherapy regimens, the patient achieved a durable complete remission (CR) which lasted till late 2010. He received Rituximab between 11/2010 and 2/2011 but due to progression on therapy, he was switched to Bendamustine, starting in 4/2011 and finishing the last cycle in 9/2011. The patient was also diagnosed with transitional cell bladder carcinoma in 2008, which was treated with surgical excision. In 10/2011, the patient developed anemia. Bone marrow biopsy on 11/17/2011 (Fig. 1) showed trilineage dysplasia with no obvious increase in blasts, consistent with therapy-related myeloid neoplasm. Karyotyping showed 46, XY, t(7;22)(q21;q12)[2]/46,XY[18]. FISH studies for MDS [del(5/5q), del(7/7q), del(20q), del(17p/TP53), trisomy 8] were normal. No obvious lymphoid aggregates were seen, but flow cytometry showed residual chronic lymphocytic leukemia/small lymphocytic lymphoma (approximately 2.5% of CD45+ cells).

The patient was treated with Azacitidine for 6 cycles until August 2012 and then received chemotherapeutic conditioning with busulfan and fludarabine, followed by an HLA matched unrelated transplant (MUD) on 8/24/2012. The patient remained in complete remission of CLL/SLL as well as MDS until 2013 when the patient reported feeling anorexic with accompanying weight loss. Esophagogastroduodenoscopy (EGD) performed 6/13 showed diffuse erythema and gastropathy throughout the stomach, particularly in the stomach fundus and antrum, with scattered petechiae and erythema in the antrum. Multiple gastric biopsies were taken which showed severe gastritis, for which he received PPI treatment, but no GVHD. Repeat EGD 2/5/2014 showed patchy erythema in the gastric body and minimal erythema in the antrum. The gastric biopsy on 02/05/2014 (Fig. 2) showed an extensive mononuclear infiltrate which could easily be confused with lymphocytes in the setting of chronic inflammation. However, given the patient's history, additional studies were performed out of an abundance of caution. Immunohistochemical studies showed the infiltrate to be positive for CD34, CD117, and myeloperoxidase consistent with myeloblasts. Therefore, in this case, MDS had relapsed as myeloid sarcoma with involvement of the gastric mucosa. Notably, bone marrow biopsy was negative for both myelodysplasia and acute myeloid leukemia.

Systemic chemotherapy is considered the mainstay treatment of even isolated MS, since progression to acute leukemia is likely if only treated locally with surgery or radiotherapy. Furthermore, the time for progression to acute leukemia is longer in those treated with systemic chemotherapy compared to local radiotherapy [15]. Therefore, the patient was started on azacitidine. Repeated EGD and gastric biopsies on 05/30/2014, 11/14/2014, and 07/30/2015 (Fig. 3) showed persistent erythema and myeloid sarcoma, while corresponding bone marrow biopsy showed no signs of MDS, AML, or CLL/SLL, in morphology, immunohistochemical studies, flow cytometry, or cytogenetic studies (Fig. 4). Unfortunately, the patient did not respond to treatment and developed host versus graft reaction of neuropathic nature leading to discontinuation of therapy. He was made hospice 4/22/2016 andexpired on 08/9/2016.

## 3. Discussion

With the introduction of reduced intensity conditioning for older patients and the use of alternative donors, SCT has increasingly become a potentially curative management strategy for MDS patients and is recommended for MDS patients prior to progression to AML. Early transplantation within 12 months of MDS diagnosis has been associated

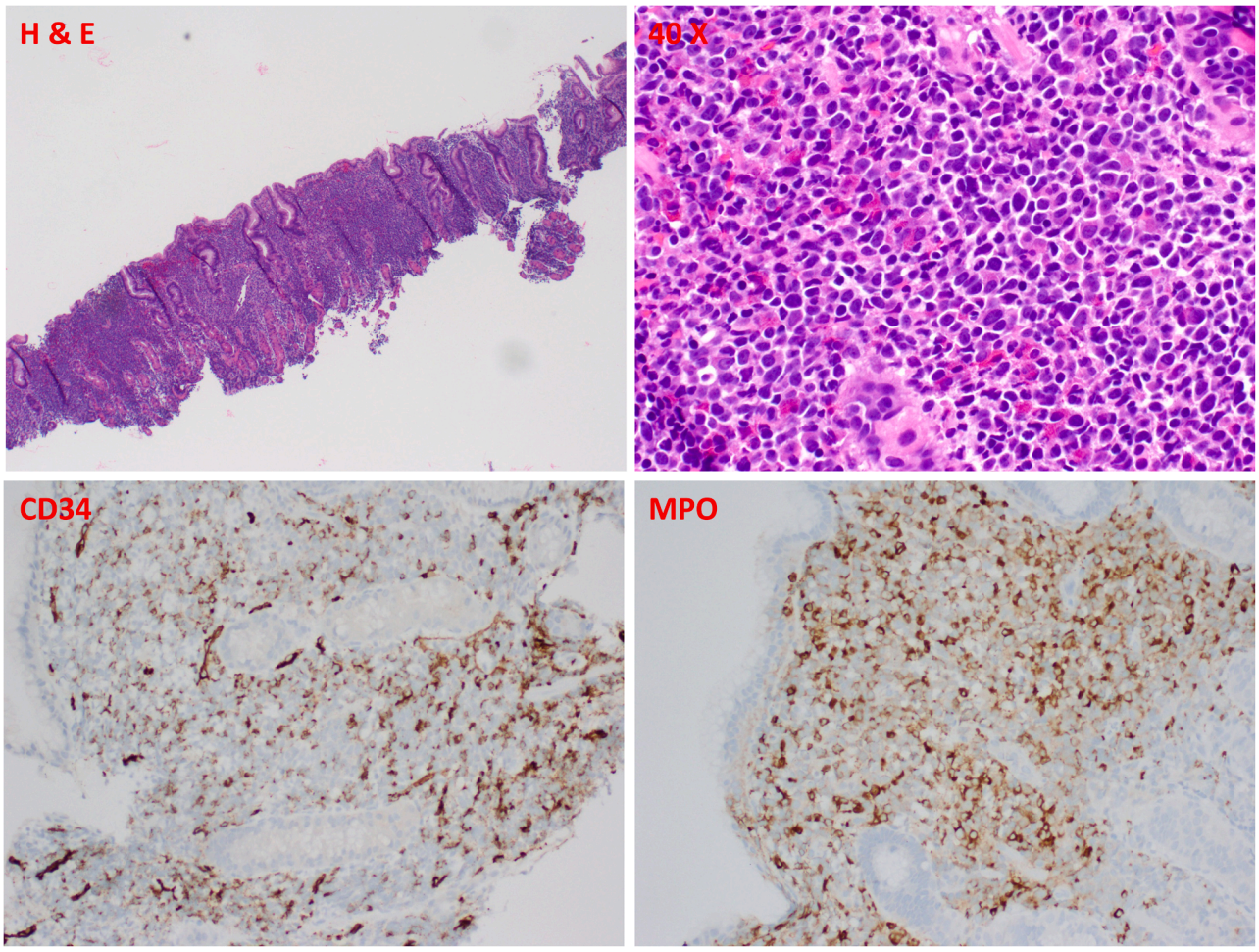


**Fig. 2.** Gastric biopsy post allogeneic SCT, showing MDS relapse as gastric myeloid sarcoma. H & E shows benign gastric mucosa with diffuse submucosal infiltrate by large atypical immature cells with fine chromatin, occasional conspicuous nuclei, and scant cytoplasm. The immature cells are positive for CD34 and myeloperoxidase, consistent with myeloblasts and the diagnosis of myeloid sarcoma.

with increased survival [16]. Different scoring systems, such as the IPSS and World Health Organization (WHO) classification-based prognostic scoring system (WPSS), have been used to predict the prognosis of MDS patients [17] with low risk patients demonstrating better clinical outcomes [6].

Myeloid sarcoma (MS) refers to an extramedullary proliferation of myeloblasts that disrupt the normal architecture of the underlying tissue. In effect, it is the tissue equivalent of AML. Myeloid sarcoma can involve any part of the body, including skin, CNS, soft tissue, bone, lymph node, and rarely, the breast, eye, heart, and nerves [8]. Myeloid sarcoma may occur due to dysfunctional homing signals for blasts [8–10, 13]. It is believed that post-transplant myeloid sarcomas develop secondary to the ability of myeloblasts in extra-medullary sites to evade immune surveillance [18].

Relapse is the most common cause of morbidity of SCT. Relapse as MS is rare for myeloid neoplasms and is mostly seen in patients with AML [8–12,19]. Relapse as MS after SCT for MDS is even more rare. To the best of our knowledge, only two studies have reported this phenomenon thus far. A study by Szomor et al. reported that 3 out of 229 (1.3%) patients transplanted for AML, CML, or MDS relapsed as myeloid sarcoma [14]. One of these patients had MDS and relapsed with MS as a pelvic mass 5 years after allogenic SCT. Overall, two of the MS cases presented in the ovaries and one in the CNS [14]. Zhang et al. also reported a patient with MDS and complex karyotype, who underwent a reduced intensity MUD, but relapsed as myeloid sarcoma two years later, as a pelvic mass without bone marrow involvement [13]. In this paper, we report the first case in which a MDS patient relapsed post-transplant as myeloid sarcoma involving the gastrointestinal tract. The relapse occurred in the stomach without bone marrow or other extra-medullary involvement 1 ½ years after allogenic SCT.

Myeloid sarcoma is deadly, with a 5 year overall survival rate of 47% highlighting the importance of making an accurate diagnosis [20]. Myeloid sarcoma can occur before, with, or after AML, MDS, or MPN diagnosis, or post-transplant for these diseases [8]. The risk of relapse in MDS is largely affected by cytogenetics, WHO classification, level of disease burden at SCT, and the conditioning regimen [6]. High cytogenetic risk is associated with higher chance of relapse. The development of myeloid sarcoma after allogeneic-SCT for AML is also reported to be associated with certain cytogenetic abnormalities, the development of graft versus host disease (GVHD), and treatment with donor lymphocytes infusion (DLI) [10].

Myeloid sarcoma usually displays myelomonocytic or pure monocytic phenotype, and stains positive for lysozyme, CD4, CD64, and occasionally, for CD34, CD117, and/or MPO. Myeloid sarcoma must be differentiated from other malignancies, one major differential being blastic plasmacytoid dendritic neoplasm (BPDCN), which stains strongly

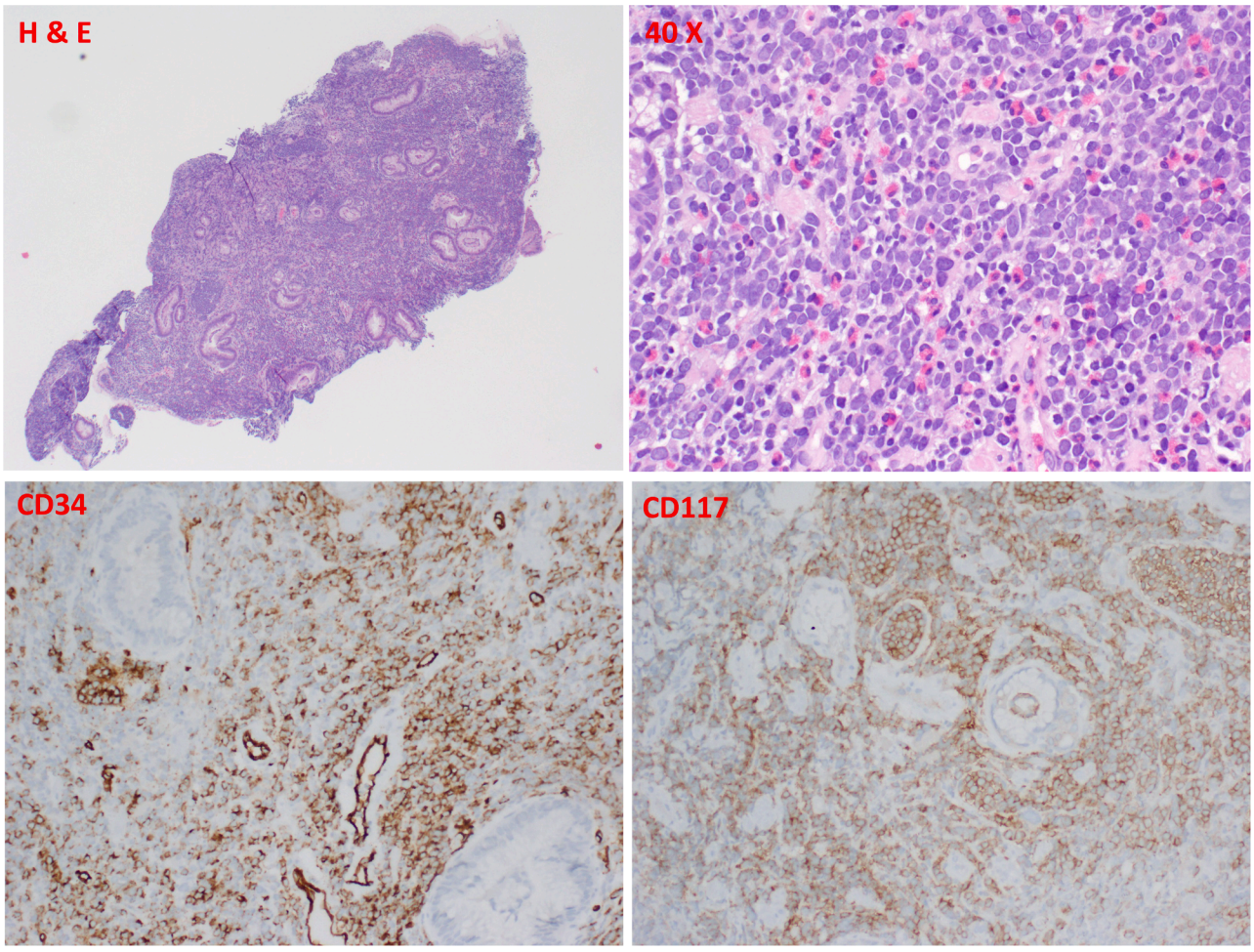


**Fig. 3.** Repeated gastric biopsy showing persistent myeloid sarcoma. H & E shows benign gastric mucosa with diffuse submucosal infiltrate of large atypical immature cells with fine chromatin, occasional conspicuous nucleoli, and scant cytoplasm. The immature cells are positive for CD34 and CD117, consistent with myeloblasts and the diagnosis of myeloid sarcoma.

positive for CD4, CD56, and CD123. Clinical correlation may be necessary to distinguish myeloid sarcoma from this differential. Myeloid sarcoma must also be distinguished from high grade lymphomas (lymphoblastic lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma) and non-hematopoietic tumors which can usually be accomplished using a battery of immunohistochemical stains that include myeloid, monocytic, and lymphoid markers [21].

The prognosis of solitary myeloid sarcoma relapse is poor, although it seems slightly better than that of bone marrow relapse alone, or combined bone marrow and extramedullary relapse [9]. As myeloid sarcoma usually progresses to involve other extra-medullary sites and the bone marrow within one year, bone marrow biopsy should also be performed to rule out marrow involvement [18]. However, relapsed myeloid sarcoma may have different phenotypes or features and may require additional treatment options.

There has been no major progress in preventing relapse in post-transplant MDS patients. It is recommended to combine local treatment (i.e., radiotherapy) with systemic therapy (i.e., chemotherapy, immunotherapy, DLI, or re-transplantation) in these patients [10]. Since most relapses occur within the first year after allogeneic SCT, pre-emptive treatment of minimal residual disease may be initiated early to prevent relapse [6]. In summary, we report the first case of GI relapse of MDS as a myeloid sarcoma post-transplant. We seek to alert our audience of this potentially serious diagnostic pitfall, particularly one that can be relatively easily resolved on the basis of immunohistochemical profiling.

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## CRediT authorship contribution statement

**Amy Song:** Data curation, Writing - original draft. **Masoumeh Ghayouri:** Conceptualization. **Farhan Hiya:** Data curation, Writing - original draft. **Mohammad O Hussaini:** Data curation, Writing - original draft.

## Declaration of Competing Interest

The Authors have no relevant conflict of interest to disclose.

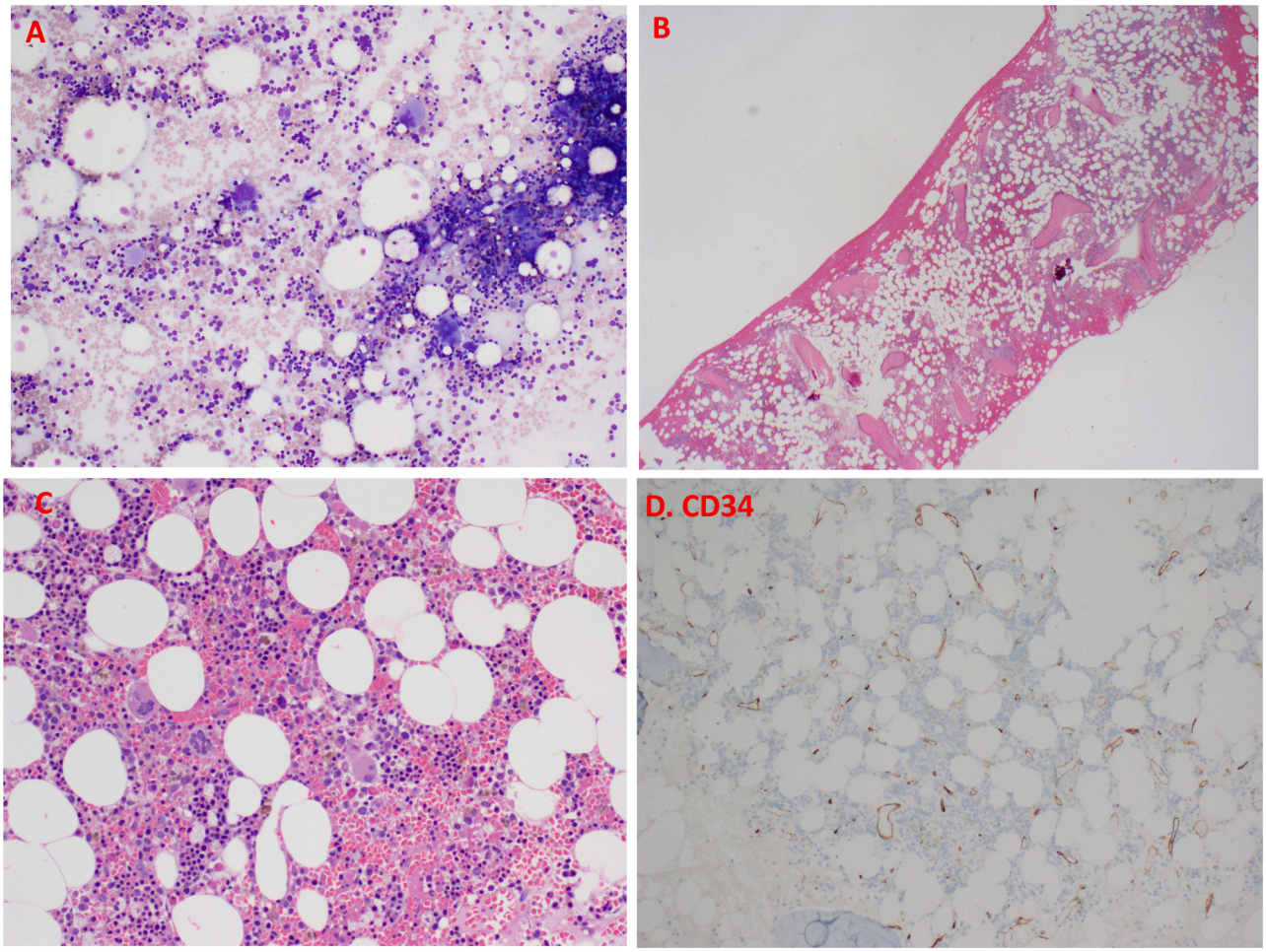


**Fig. 4.** Bone marrow biopsy post allogeneic SCT, concurrent with gastric myeloid sarcoma showing no bone marrow involvement. A. The aspirate smear shows normal trilineage hematopoiesis with no obvious evidence of dysplasia or increase in blasts. B. The bone marrow is mildly hypocellular with mild trilineage hypopasia. **C.** Higher power view of the bone marrow shows trilineage hematopoiesis with no obvious dysplasia or increase in blasts. D. Immunostain for CD34 shows blood vessels but no increase in blasts. Therefore, no MDS relapse or AML were detected in the bone marrow.

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