Primary peritoneal myeloid sarcoma in association with CBFB/MYH11 fusion

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ABSTRACT

Myeloid sarcoma, also known as chloroma or granulocytic sarcoma is an extramedullary disease process that typically presents in association with acute myeloid leukemia during initial presentation or at relapse. Often associated with cytogenetic mutations, including t(8;21)(q22;q22); RUNX1/RUNX1T1, and less frequently with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB/MYH11, myeloid sarcoma is most commonly discovered in skin, soft tissue, bone, and connective tissue. In rare circumstances, myeloid sarcoma can present without any evidence of bone marrow or leukemic involvement. These cases of de novo myeloid sarcoma are rare, and are commonly misdiagnosed due to similarities with other entities. We report an unusual case of a primary de novo peritoneal myeloid sarcoma, in association with inv(16)(p13.1q22) and clonal heterogeneity at different sites of involvement, that has responded well to AML induction therapy and consolidation treatment with gemtuzumab ozogamicin and high dose cytarabine. Cytogenetics, immunophenotyping, and chromosomal analysis, were each critical in establishing a proper diagnosis as well as helping to develop appropriate therapeutic strategies for this rare entity.

1. Introduction

Myeloid sarcoma (MS), also known as chloroma or granulocytic sarcoma is a distinct entity in the WHO classification. Although it is most often reported in association with findings consistent with acute myeloid leukemia (AML) in the blood or bone marrow, MS can also be found as a sign of disease progression to a more aggressive form in other conditions, including myelodysplastic syndrome, chronic myelogenous leukemia, chronic myelomonocytic leukemia, and myelofibrosis [1-3]. It is typically discovered as a rare manifestation of AML consisting of extramedullary proliferation of immature myeloid blast cells with disruption of the normal architecture of the invaded tissue. MS can involve any site in the body, but in one National Cancer Database analysis, MS was most commonly found in connective and skin tissue (31%), skin and breast (12%), the digestive system (10%), lymph nodes (10%), bone and joints (6%), and the nervous system (6%) [4]. Tumors of the genitourinary and gastrointestinal system are noted to carry a better prognosis than those involving the nervous system, soft tissue, and lymph nodes [5]. MS most often presents either as part of the presentation of AML or during relapse following treatment of AML.

Occurring in 2.5–10% of AML patients, MS is typically an easy diagnosis to make due to a known history of AML. In rare circumstances, however, MS can occur without any evidence of bone marrow involvement rendering the diagnosis more difficult to establish. Due to their infrequent nature, cases of primary de novo MS are limited to a small number of case reports and case series and are sometimes only discovered at autopsy [6]. Various chromosomal aberrations have been found in association with MS, including monosomy 7, inv(16)(p13.1q22), t(8;21)(q22;q22), RUNX1/RUNX1T1, and less frequently with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB/MYH11 [5]. We hereby report a rare case of primary de novo peritoneal MS associated with inv(16) in a patient who was subsequently treated with 7 + 3 AML induction therapy (cytarabine and daunorubicin) and received consolidation treatment with gemtuzumab ozogamicin (GO) and high-dose cytarabine.

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2. Case presentation

A previously healthy 42 year old male presented with progressive abdominal pain, early satiety, and increasing abdominal distention over the course of 2 months. CBC, CMP, and LDH were all within normal limits. Computed tomography imaging (CT) of the chest and abdomen demonstrated the presence of an ileocecal mass (Fig. 1) as well as notable mesenteric lymphadenopathy.

A colonoscopy was performed and revealed evidence of external compression to the lumen of the cecum without evidence of an intraluminal mass. The patient underwent subsequent right hemicolectomy including terminal ileum resection. Pathology examination revealed a large mass in the retroperitoneum invading through the serosa into the muscularis propria and lamina propria. The neoplastic cells were mononucleated with open chromatin and multiple nucleoli; mitosis and apoptosis were easily identified (Fig. 2A). A large battery of antibody panel was then utilized for immunohistochemistry studies. The neoplastic cells were positive for myeloperoxidase (Fig. 2B), CD68 (PGM1) (Fig. 2C), CD34, CD117, and BCL2; negative for multiple markers targeting lymphocytic, histiocytic, epithelial, or melanocytic malignancies, including PAX5, CD3, TdT, pancytokeratin, SOX10, and BerEP4. These findings favored myeloid sarcoma with monocytic differentiation.

Conventional karyotyping was not carried out on the specimen due to lack of fresh tissue for proper testing. A bone marrow biopsy was performed and demonstrated trilineage hematopoiesis with no evidence of acute myeloid leukemia. Postoperative course was complicated by wound dehiscence and surgical-site infection requiring a prolonged course of antibiotics and placement of a surgical vacuum drain, delaying initiation of systemic chemotherapy.

Two months following surgery, while still recovering from the surgical site infection, the patient presented to the hospital with worsening abdominal pain, abdominal distension, nausea and constipation. A CT of the chest and abdomen showed diffuse peritoneal deposits, moderate ascites, and interval development of lymphadenopathy in the retroperitoneum, pelvis, and chest. Cytological examination of the ascitic fluid revealed CBL gene mutation. Repeat bone marrow biopsy showed no evidence of acute leukemia by morphology, flow cytometry analysis, and FISH study.

The patient subsequently commenced 7+3 induction therapy with daunorubicin (90 mg/m2) on days 1–3 and cytarabine (100 mg/m2) on days 1–7. On day 3 of induction, his presenting symptoms of abdominal pain, distention and nausea started resolving. Restaging imaging with MRI performed 6 weeks after induction therapy demonstrated near resolution of peritoneal deposits as well as improved lymphadenopathy. After a delay in obtaining tissue biopsy results, the patient subsequently commenced consolidation therapy with high dose cytarabine (3 g/m2 q12 h on days 1, 2, and 3) and gemtuzumab ozogamicin (3 mg/m2) and received his second cycle two months later. Due to prolonged neutropenia complicated by sepsis requiring hospitalization following the first two cycles of consolidation therapy, the plan is to administer a lower dose of cytarabine (1.5 g/m2) without gemtuzumab for cycles 3 and 4 of consolidation therapy in order to avoid prolonged neutropenia and further risk of infection. The patient recently completed his third dose of consolidation therapy with cytarabine alone, and he continues to do well without evidence of disease progression.

3. Discussion

De novo isolated MS is a rare entity with limited reports in the literature discussing presenting features, management and prognosis. In addition, reports on cytogenetic and molecular characteristics are lacking. De novo MS has been found to progress to AML on a median of 6–12 months [6]. With rates of misdiagnosis ranging between 25 and 40%, primary de novo MS is an extremely difficult diagnosis to establish due to its clinical and histological similarities with other entities (e.g., high-grade lymphoma, medulloblastoma) [5,7]. Carrying nonspecific radiographic findings, a proper diagnosis of isolated MS cannot be accurately made without the utilization of immunohistochemical and immunophenotyping modalities accompanied by a high index of suspicion. Cytogenetic and molecular analyses are also frequently missed due to improper handling of the specimens, but such insights provide important data regarding the pathophysiology of the disease and help provide a potential window for use of targeted therapies.

Our case also revealed discrepancies in karyotype when comparing the peritoneal deposits and the free cells in the ascitic fluid, with a more complex karyotype discovered in the ascitic cells, possibly indicating...
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The evolution of a more aggressive clone. One previous study has demonstrated nearly a 30% discordance between FISH studies of different types of MS and conventional cytogenetics of the bone marrow, suggesting that cytogenetics with FISH is critical during the investigation of MS [5]. Inv(16) has especially been shown to share an strong association with MS of the gastrointestinal tract, mesentery and peritoneum. This aberration down regulates the core binding transcription factor (CBF), which is believed to be a possible mechanism of disease progression in MS, especially for those involving the GI tract. This inversion leads to the fusion of two genes on chromosome 16, \textit{CBFB} and \textit{MYH11}, which in turn leads to the formation of a protein that prevents CBF from binding to DNA. The fused genes ultimately block the differentiation of blood cells, leading to the production of abnormal myeloid blasts in MS. Despite the favorable prognostic value in AML, the impact of \textit{MYH11/CBFB} fusion in MS cases remains unclear [8].

Because surgical resection and local radiotherapy have proven unable to delay the progression of de novo MS to AML, systemic chemotherapy is the current standard treatment of choice in primary de novo MS. Although there are no prospective randomized trials comparing treatments for primary de novo MS, case series and retrospective studies support the notion that standard AML chemotherapy is the most effective therapy not only in delaying progression of de novo MS to AML, but also in improving overall survival [9].

Although there are no prospective trials examining the efficacy of allogeneic hematopoietic cell transplantation (allo-HSCT) in primary de novo MS patients, retrospective data has demonstrated improvement in overall survival in MS patients who underwent allo-HCT following AML induction chemotherapy [10]. In our case, the patient did not undergo allo-HSCT due to his favorable risk stratification with CBF induction and high dose cytarabine alone [11].

Data is still lacking and no prospective trials have examined the role of targeted therapy against de novo primary MS. Several cases have reported complete and relatively sustained remissions in patients with isolated MS when treated with GO [12]. The decision to use GO in our case was supported by improved outcomes in AML patients with core binding factor mutations [13], and suggests that cytogenetic factors perhaps supersedes extramedullary AML for risk stratification in such patients.

**Author contributions**

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**Informed consent**

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