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Widespread myeloid sarcoma with KMT2A rearrangement involving the testis, oral cavity, heart, kidney and gallbladder without bone marrow involvement

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ABSTRACT

Myeloid sarcoma is a solid hematological tumor consisting of growing immature myeloid cells in tissues outside the bone marrow. Myeloid sarcoma presenting before the onset of bone marrow disease is rare. Here, we report the case of a young 35-year-old male who presented with testicular mass and was diagnosed with widespread myeloid sarcoma involving internal organs like heart, kidney and gallbladder. Peripheral blood and bone marrow examination did not show any evidence of leukemia. Genetic analysis was significant for KRAS G12D mutation and KMT2A rearrangement. Induction chemotherapy for extramedullary AML with cladribine, cytarabine, GM-CSF and idarubicin (CLAG-IDA) achieved complete remission. However, the patient relapsed after 2 months and developed rapidly progressive disease. The disseminated nature of the disease in a patient without bone marrow involvement are what make this case extremely rare. Involvement of organs like heart, gall bladder and kidney is also uncommon. Isolated myeloid sarcoma is a challenge to diagnose as there are no manifestations of leukemia in peripheral blood or bone marrow, so it is usually not considered among the differential diagnoses. KM2TA rearrangement identified on genetic analysis is a rare finding in patients with AML and is associated with poor outcomes. KRAS mutations are currently being studied as therapeutic targets in these patients. This case report describes the detailed diagnostic process and discusses the possible strategies for diagnosis and treatment that can be used in similar cases.

1. Introduction

A tumor mass consisting of myeloid blasts, occurring at a site other than the bone marrow, is diagnosed as myeloid sarcoma (MS) [1]. It can present as an isolated tumor with no evidence of hematological malignancy (isolated MS). More commonly, it presents concurrently with or at relapse of acute myeloid leukemia (AML). It is commonly known as chloroma or granulocytic sarcoma. It usually occurs in patients with AML but can also present in patients with myelodysplastic syndrome or myeloproliferative neoplasm. MS, when associated with AML, is usually diagnosed concomitantly with AML or after the diagnosis of AML [2–4]. Because of the absence of blood and marrow manifestations, isolated MS is a diagnostic challenge and is often misdiagnosed as another disease, most commonly as a lymphoma [5].

MS can develop anywhere in the body but is most commonly reported in the lymph nodes, skin, soft tissue and bone [5]. Involvement of internal organs like heart, gallbladder and kidney is very rare. Isolated MS usually occurs in one or two sites and widespread disease is usually associated with AML. Here, we present a case of widespread MS involving uncommon sites like testis, oral cavity, heart and kidney without any bone marrow involvement.

2. Presentation

We present a 35-year-old male with no significant past medical history who presented to the ED for evaluation of testicular swelling along with pain since the past 4 weeks. He also had a weight loss of 5 pounds in the last month. On exam, a firm, oblong mass could be appreciated in the upper pole of the right testicle which was tender to palpation. A Computed Tomography scan of Thorax/Abdomen/Pelvis was ordered which showed 2.9 × 2.2 cm extratesticular lesion abutting the right epididymis, likely inflammatory or infectious collection, with no other lesions observed elsewhere. Labs showed white blood cell count was 4920/μl, hemoglobin was 14.0 g/dL and platelet count was 211,000/μl.

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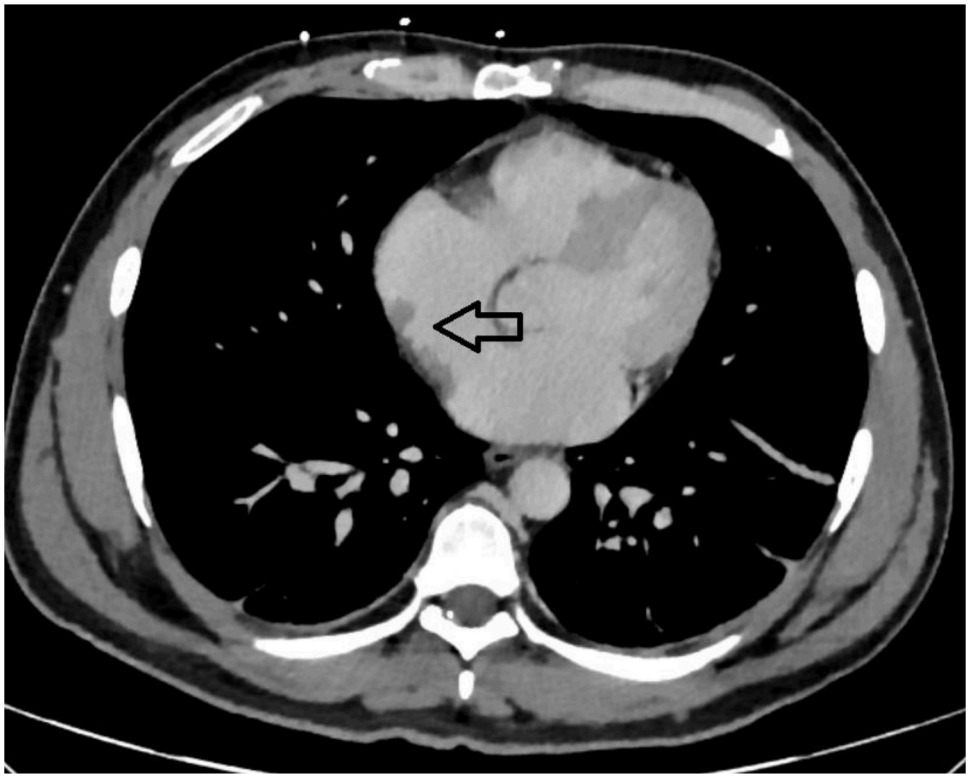

Fig. 1. CT thorax shows 10 mm nodule along the lateral wall of the right atrium in the region of the crista terminalis (black arrow).

LDH was 187 U/L. A comprehensive metabolic panel showed normal liver and kidney functions. Urinalysis was not suggestive of an infection. Alpha fetoprotein level was normal. We consulted the urology team and made a decision to treat empirically for infection with Ciprofloxacin and monitor the swelling outpatient but the patient did not follow up.

About 2 months later, the patient presented to his dentist with a swelling inside his mouth for the past 4 weeks along with night sweats and weight loss. On exam, there was a lesion on the left side, extending from distal portion of tooth #15 to the hamular notch. Lesion was erythematous and white, indurated, not purulent and non-tender to palpation. A biopsy was done which on hematoxylin and eosin staining showed a diffuse infiltrate of atypical mononuclear cells with blastic morphology. Immunostaining was positive for CD68, CD34, CD117, CD33, CD43 and HLA-Dr. These results were suggestive of extra-medullary MS and the patient was admitted to our hospital. Here, MRI of the face/neck/orbit showed a lesion in left upper maxillary gums with

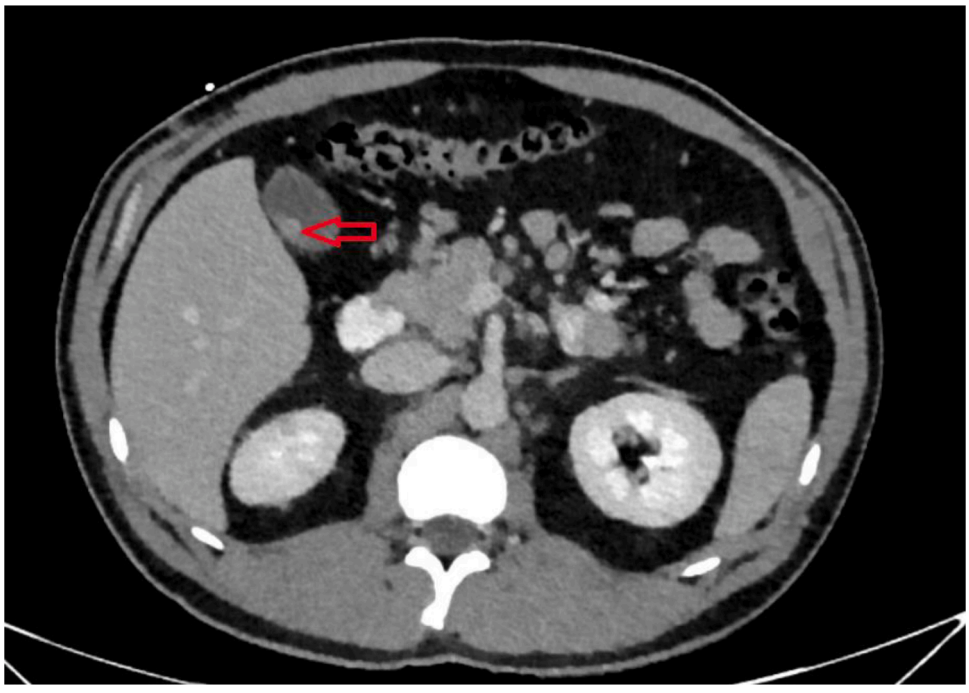

Fig. 2. CT shows 6 mm soft tissue nodule in the posterior gallbladder (red arrow).

extension into soft and hard palate with multiple enlarged lymph nodes, concerning for metastasis.

Also, repeat ultrasound of scrotum showed interval increase in size of testicular mass. Right sided orchiectomy was performed, immunostaining results from the mass showed an immature myeloid population (~11%of total) expressing CD13 (dim), CD33, CD34, CD117, HLA-DR. (dim), CD4, CD11c, and CD38. The findings were consistent with extramedullary myeloid sarcoma involving the testis. The KMT2A (MLL) rearrangement was detected on FISH and KRAS G12D was detected on next generation sequencing. Standard prognostic molecular markers including FLT-3, NPM-1 and CEBPA were negative. Cytogenetics were also negative for t(8;21) and inv(16). Bone marrow biopsy was performed which showed no overall immunophenotypic evidence of acute leukemia, non-Hodgkin lymphoma or high-grade myelodysplasia. At this time as well, all blood counts were within normal range.

CT Thorax/Abdomen/Pelvis was performed which suggested that disseminated disease had developed (as compared to previous CT scan 2 months ago), most pronounced within the mesentery, retroperitoneum, and subcutaneous tissues. Additional sites of suspected metastasis included an anterior pericardial lymph node, the right atrium (Fig. 1), right kidney, adrenal glands, and the gallbladder (Fig. 2). Patient was started on induction chemotherapy with cladribine, cytarabine, G-CSF and idarubicin (CLAG-IDA) for extramedullary AML. This included cladribine 5 mg/m^2 IV on days 1–5, cytarabine 2 gm/m^2 IV on days 1–5, G-CSF 300 mg subcutaneous on days 1–5, idarubicin 12 mg/m^2 on days 1–3. The plan was to induce remission and continue this regimen for 3–4 cycles for consolidation. This is a standard regimen used at our center for newly diagnosed high-risk AML. Patient underwent complete remission with this treatment after 2 cycles which was confirmed on repeat CT imaging. However, about 2 months later, while on consolidation chemotherapy, he unfortunately relapsed with development of new skin lesions as well as involvement of peripheral blood and bone marrow. He had rapidly progressive disease which led to multiorgan failure and subsequent death. Because the patient worsened very quickly, no other treatment modality could be tried.

3. Discussion

MS is seen in 2.5%−9.1% of AML cases [6]. Isolated MS is characterized by biopsy-proven growth of immature myeloid cells in the absence of a history of leukemia (commonly AML), myeloproliferative neoplasm or myelodysplastic syndrome and a negative bone marrow biopsy [2–4]. MS can also be a manifestation of relapse in a previously treated patient with AML in remission [5].

MS can affect all age groups, with cases being reported in patients from 2 to 81 years old [6]. Lymph nodes, soft tissues and bone are the most prevalent sites of biopsy-proven involvement of MS. Other areas where MS has been reported include central nervous system (CNS), oral and nasal mucosa, breast, genitourinary tract, retroperitoneum, chest wall, pleura and testis [5,7]. Our patient came with multi-system involvement including heart, kidney and gall bladder which is very rarely seen. Clinical manifestations are diverse and dependent on the sites involved. Diagnosis of MS is challenging, particularly in the absence of bone marrow disease and usually requires radiological imaging along with tissue biopsy [1]. Computerized tomography (CT), magnetic resonance imaging (MRI), flourodeoxyglucose positron emission tomography (FDG-PET) are commonly used imaging studies for localizing tumors and assessing response to treatment, with CT usually being the test of choice as MS usually involves soft tissues. FDG-PET is useful for planning radiation and monitoring response to therapy.

Karyotyping and fluorescent in-situ hybridization (FISH) are commonly used to determine the cytogenetic and molecular properties of the tumors. The most common cytogenetic abnormalities associated with MS include translocation t(8;21) and inversion of chromosome 16 (inv 16)[4,5]. Our patient had the KMT2A (MLL) rearrangement detected on FISH and K-RAS detected on next-generation sequencing. Some studies suggest that patients with MS have a higher prevalence of RAS mutations as compared to patients with AML [8]. KMT2A rearrangement is associated with adverse outcomes in patients with AML [9].

Isolated MS usually leads to AML within a median time period of 5–12 months [6,10]. Treatment of both isolated MS and MS associated with AML is done with conventional AML-type chemotherapeutic protocols using cytarabine and anthracyclines. This is because there is a higher tendency of progression to AML in isolated MS patients receiving localized therapy versus those receiving systemic chemotherapy [10]. In patients having isolated MS treated with AML-type chemotherapy, complete remission rates are similar to patients having AML without MS [10]. Radiation therapy is used in those patients with isolated MS who have not achieved complete regression of tumor mass after chemotherapy. It can also be used as a means of palliative treatment to relieve compression symptoms (spinal cord compression, superior vena cava compression). In such cases, radiation therapy can be used upfront, followed by aggressive chemotherapy. Surgery can also be used to relieve compression and also when excision biopsy is necessary for diagnosis.

4. Conclusion

We report the case of a patient with widespread myeloid sarcoma without bone marrow involvement, who initially presented with a testicular mass. MS is a rare disease and is often misdiagnosed, especially when occurring before the development of AML. MS should be considered on the differential for patients having multiple soft tissue or bone lesions, even when there is no obvious bone marrow involvement. Tissue biopsy should be urgently performed and specimens should undergo immunostaining as well as karyotyping. KRAS mutations can explain the tropism of myeloid blasts for extramedullary tissues. KMT2A mutations are associated with adverse outcomes. It is essential that MS be diagnosed early, definitively and systemic chemotherapy be started at once. We used CLAG-IDA for this patient and this patient showed a positive response with interval reduction in disease burden. Radiological examination is also used to monitor response to systemic chemotherapy. The prognostic significance of MS in patients with AML is not clearly understood and requires more robust and large scale studies.

Declaration of Competing Interest

The authors of this article have no competing interests to declare.

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