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Case Report

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Secondary Cutaneous Myeloid Sarcoma Treated with Nanoliposomal Encapsulation of Daunorubicin and Cytarabine

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Abstract

Cutaneous myeloid sarcoma is a rare malignancy and most often arises in the setting of acute myeloid leukemia. Here, we present the unique case of a patient who developed secondary cutaneous myeloid sarcoma after developing myelodysplastic syndrome from breast cancer treatment. We describe complete resolution of her lesions after treatment with a nanoliposomal dual encapsulation of daunorubicin and cytarabine and to our knowledge the first known treatment of a patient with cutaneous myeloid sarcoma with this regimen.

Keywords

Myeloid; Sarcoma; Breast cancer; Cytarabine; Nanoliposomal

Introduction

The diagnosis of AML and myeloid sarcoma are similar with one key exception: myeloid sarcoma consists of extramedullary myeloid blasts that develop into a mass by effacing normal tissue architecture. The WHO has set out guidelines for the diagnostic terminology and criteria of myeloid sarcoma and other names have also been used in the diagnosis: granulocytic sarcoma, extramedullary myeloid tumor, or chloroma. The most frequent sites of involvement are the skin, lymph nodes, gastrointestinal tract, bone, soft tissue, and testis. Other sites can also be involved.

Diagnosing myeloid sarcoma presents a challenge, particularly if the patient doesn't present with a known hematological disorder. The clinical presentation, radiographic images, immunohistochemical results, and cytogenetic markers all should be taken into account during the diagnostic process. Morphologically myeloid sarcoma appearance is the same as AML with blast forms, high nuclear-to-cytoplasmic ratios, fine chromatin and prominent nucleoli.

Case Presentation

A 68-year old woman with a past medical history of vitiligo and lobular carcinoma of the breast treated with lumpectomy, adjuvant chemotherapy, radiation therapy, and tamoxifen for 5 years presented to the clinic with multiple, intermittently appearing, pink firm papules and nodules on multiple areas of the body including: right forehead, left neck, bilateral posterior shoulders, back and upper extremities (Figure 1). Skin biopsy of one of the nodules was consistent with the diagnosis of myeloid sarcoma (Figure 1). A bone marrow biopsy was performed and she was found to have myelodysplastic syndrome with multi-lineage dysplasia, however, there was no evidence of leukemia. Next generation sequencing panel was performed on the cutaneous lesion which showed mutations in *NPM1, DNMT3A*, as well as *KRAS* and *FLT3* mutation negative.

Thus it was concluded that she had a secondary entirely cutaneous myeloid sarcoma which developed after breast cancer therapy. This has never been reported before in the literature hence no standard treatment protocols exist. Treatment with a dual encapsulated daunorubicin and cytarabine nanoliposomal formulation was selected based on its approval in the setting of therapy related Acute Myeloid Leukemia (AML) in patients ≥ 60 years old as it has shown an improved median overall survival benefit compared to the standard combination of daunorubicin and cytarabine (7+3 regimen) [1]. Her treatment course thus far has included: induction chemotherapy with the same dosing used in the clinical trial (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 on day 1, 3 and 5). Following induction therapy, she developed neutropenic fever from which she recovered. After induction chemotherapy, the cutaneous nodules completely resolved. Two cycles of consolidation therapy were performed with two days of chemotherapy rather than three days. The consolidation therapy was well tolerated.

A bone marrow biopsy at four months, again showed no evidence for therapy-related myeloid leukemia. She is now more than a year after her initial diagnosis of cutaneous myeloid sarcoma and is without evidence of disease. One more additional bone marrow biopsy is planned.

Discussion

This case is unique as it is the first reported case of secondary cutaneous myeloid sarcoma arising in the setting of myelodysplasia due to breast cancer therapy. Additionally, experience with therapy for secondary cutaneous myeloid sarcoma in this setting is limited without prior reports.

The diagnosis of AML and myeloid sarcoma are similar with one key exception: myeloid sarcoma consists of extramedullary myeloid blasts that develop into a mass by effacing normal tissue architecture [2]. The WHO has set out guidelines for the diagnostic terminology and criteria of myeloid sarcoma and other names have also been used in the diagnosis: granulocytic sarcoma, extramedullary myeloid tumor, or chloroma [3]. The most frequent sites of involvement are the skin, lymph nodes, gastrointestinal tract, bone, soft tissue, and testis. Other sites can also be involved [4].

Cutaneous myeloid sarcoma can arise in the setting of AML, relapse of AML, through blast transformation in chronic myeloproliferative syndrome or myelodysplasia, or de novo. In one small case series, the diagnosis was most likely simultaneously seen with AML or AML developing after diagnosis (within 10.5 months on average) [3,5]. In the case of the patient presented here, it appears her cutaneous

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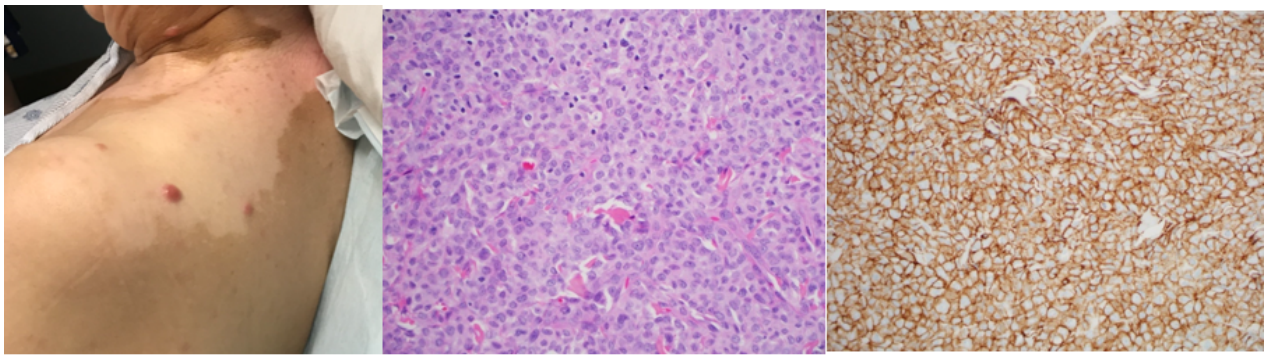

Figure 1: (Left) Initial dermatological manifestation of myeloid sarcoma. Left shoulder with multiple, pink, firm, papules and nodules; (Middle) Hematoxylin and Eosin (H and E) stain showing fairly monotonous, packed, non-gland forming population of cells with large nuclei, open chromatin, irregular nuclear contours, frequent mitotic figures, and a moderate amount of eosinophilic cytoplasm; (Right) Immunohistochemical staining of CD43 showing diffuse and strong staining.

myeloid sarcoma arose is the setting of myelodysplasia. However, it is peculiar that repeat bone marrow biopsy did not show evidence of myelodysplasia or myeloid leukemia. Thus, it may be possible that the myelodysplasia initially identified in the bone marrow was transient.

Diagnosing myeloid sarcoma presents a challenge, particularly if the patient doesn't present with a known hematological disorder. The clinical presentation, radiographic images, immunohistochemical results, and cytogenetic markers all should be taken into account during the diagnostic process [6]. Morphologically myeloid sarcoma appearance is the same as AML with blast forms, high nuclear-to-cytoplasmic ratios, fine chromatin and prominent nucleoli. Immunohistochemical results of myeloid sarcoma are identical to AML, thus stains such as CD34 and CD117 are employed to identify immature cells and MPO, CD68/KP1, lysozyme, CD33, CD14, CD43, CD168 as well as others are used to determine if the cell type is myeloid or monocytic [7,8]. Some of the more common cytogenetic abnormalities seen in myeloid sarcoma are: monosomy 7 and 16, trisomy 8, trisomy 11, Mixed Lineage Leukemia (MLL) gene rearrangements, inversion of chromosome 16, as well as 16q, 5q, and 20q deletions [8]. Additionally, mutations in Nucleophosmin (NPM) 1 have been noted in cases of myeloid sarcoma [9]. This patient had a pathological mutation in *NPM1* but not in *FLT3* gene which is favorable in AML and may have improved outcomes with high-dose induction therapy [10-12]. She also had a mutation in *DNT3A* which is also associated with improved outcomes when treated with high dose daunorubicin therapy [11].

Treatment options in myeloid sarcoma involve chemotherapy, surgical resection, allogenic hematopoietic stem cell transplant, and radiation therapy with chemotherapy being the most common modality [6]. Due to her age and her funding status, she was not a candidate for allogenic stem cell transplant. Since no therapeutic guidelines exist for secondary myeloid sarcoma, it was hypothesized that since myeloid sarcoma shares many pathologic and genetic characteristics with AML, she could benefit from a regimen used for AML.

The decision was made to treat with the dual drug nanopliposomal encapsulation of daunorubicin and cytarabine. This formulation was recently approved following a phase 3 clinical trial showing improved overall survival (9.56 v 5.95 months) in patients 60-75 years old with secondary acute myeloid leukemia compared to standard of care cytarabine plus daunorubicin (7+3) chemotherapy. Similar adverse events were seen in both arms [1]. Current NCCN guidelines give this therapy a category 1 recommendation for induction therapy for therapy-related AML and category 2A recommendation for consolidation therapy. There have been no reported cases of secondary myeloid sarcoma treated with this therapy. However, it was extrapolated that the same properties which make this formulation successful at treating secondary AML should prove beneficial in secondary cutaneous myeloid sarcoma. The improved cytotoxicity demonstrated toward cancer cells in preclinical models stems from the ability of the dual-drug liposomal encapsulation of cytarabine and daunorubicin to deliver a 5:1 drug ratio to cancer cells. This fixed ratio has been reported to have synergistic activity in killing cancer cells [13].

The prognosis of myeloid sarcoma is difficult to reliably determine due to the limited number of cases published. From one study, there is no significant difference in prognosis whether the myeloid sarcoma is secondary or arises de-novo. Reported overall survival had a broad range from 2 months to 10 years [2].

Conclusion

In this case report we presented a rare case of secondary cutaneous myeloid sarcoma following breast cancer therapy. We also discussed the first reported use of a dual-drug nanopliposomal encapsulation of daunorubicin and cytarabine for the treatment of secondary cutaneous myeloid sarcoma with overall positive results.

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