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Case Report

Granulocytic sarcoma presenting as a palpable breast lump in a 13-year-old female as a relapse of AML

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ABSTRACT

Granulocytic sarcoma, also known as myeloid sarcoma or chloroma, is a neoplasm of the myeloid cells that can arise before, concurrent with or following haematolymphoid malignancies, mostly associated with Acute Myeloid Leukaemia (AML). It is an uncommon extramedullary manifestation of AML. We report the case of a 13-year-old girl who presented with a painless lump in her breast. Her past medical history revealed AML, treated and considered in remission. A biopsy was performed in the palpable mass and the histopathological findings were consistent with a Granulocytic sarcoma of the breast, which was considered as a relapse of AML.

1. Introduction

Granulocytic sarcoma (GS), also known as Myeloid Sarcoma or chloroma, is a rare extramedullary manifestation of haematological malignancies of myeloid origin. It is most commonly associated with Acute Myeloid Leukaemia (AML). GS is characterised by the formation of clinically evident tumours containing immature myeloid cells in the extramedullary sites, commonly involving the skin, soft tissues, CNS and the urogenital tract. GS involving the breast is relatively rare and accounts for about 8% of cases.

Here, we report the case of a 13-year-old female, a known case of AML, post completion of chemotherapy who presented with a breast lump, which turned out to be relapse of AML.

2. Case Report

2.1. The patient

A 13-year-old female presented in January 2020, to a tertiary care hospital with a painless lump in her right breast, noticed by her 02 days ago. On evaluation, she was known to have a history of AML with CD1 and CD56 expression and t(8;21), diagnosed in April 2019. She received chemoradiotherapy for the same until November 2019, following which she underwent bone marrow and CSF evaluation, which indicated remission.

2.2. On examination

The lump was present in the lower outer quadrant of the breast. It was a firm palpable mass measuring approximately 4x3cm and was non tender. It wasn't associated with overlying skin changes or axillary lymphadenopathy.

2.3. FNAC examination

FNAC was done for initial evaluation, which revealed cellular smears with presence of a monomorphous

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population of scattered atypical cells with no normal gland formation. These cells had absent to scant cytoplasm with a high N:C ratio, marked nuclear anisonucleosis with irregular nuclear membrane and prominent nucleoli. The overall features were suggestive of a haematolymphoid malignancy. HPE was advised in this patient for further characterization of the lesion (Figure 1).

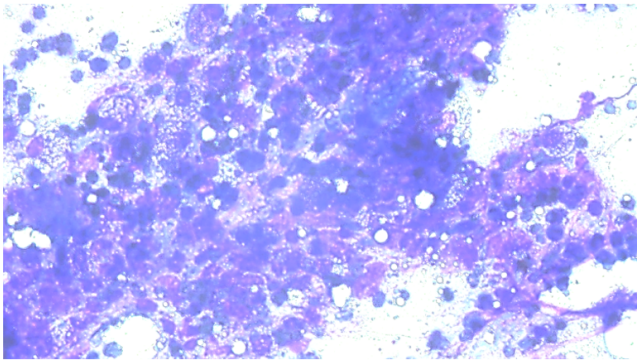

Fig. 1: FNAC smears (400x) from the breast lump reveal a monomorphous population of cells showing nuclear anisonucleosis and a high N:C ratio

She also underwent an X-ray examination of her chest, which showed normal rib cage and lung fields. Since FNAC reports were suggestive of haematolymphoid malignancy in a case of AML, the sonomammography wasn't carried out in this patient and instead, patient was taken for surgical excision of the lump.

Simultaneously, she also underwent a complete haematological examination. Peripheral blood smear showed 08% blasts (Figure 2). Bone marrow examination revealed 61% blasts of myeloid lineage (Figure 3), which was consistent with relapse of AML. On excision, the breast lump was sent for histopathological examination.

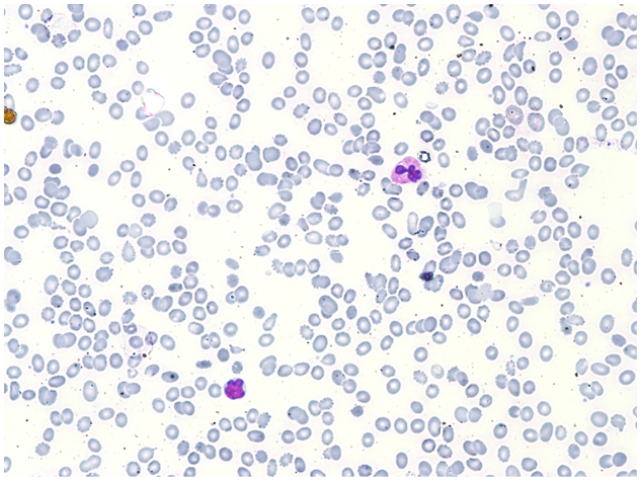

Fig. 2: Peripheral blood smear showing a single blast along with a neutrophil (400x)

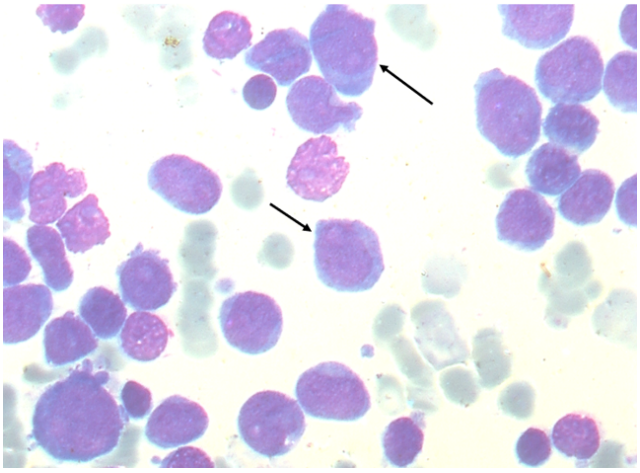

Fig. 3: Bone marrow aspirate smear reveals blasts of myeloid lineage along with few cells of erythroid series (1000x)

2.4. Grossly

The lump appeared as a fibrofatty tissue mass measuring 4x3x1.5cm. The external and cut surface was smooth and yellowish white with a greenish tinge. No lobulations or raw areas noted on the surface. No areas of haemorrhage or necrosis were seen (Figure 4).

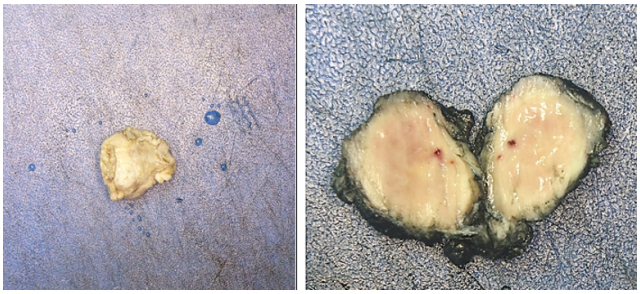

Fig. 4: The excised breast lump. The external surface is smooth. The cut surface is yellowish white with a greenish tinge

2.5. On microscopic examination (Figure 5)

The sections from the lump revealed an unencapsulated tumour composed of monomorphic population of cells, predominantly composed of blasts along with a few mature and immature granulocytes. These blasts had scant to moderate cytoplasm with occasional granularity. A high N:C ratio was seen, with oval to round nuclei with marked anisonucleosis and a vesicular chromatin. Inconspicuous nucleoli were present in some cells. Few mitotic figures were noted, along with presence of atypical mitoses. Periphery of the tumor showed scanty normal breast parenchyma with TDLUs. On immunohistochemistry with anti-myeloperoxidase (MPO) antibodies, the tumor

cells showed strong cytoplasmic positivity (Figure 6). On further immunohistochemical analysis, the tumour cells also reacted strongly to antibodies against CD43, CD56, CD68, LCA, CD99; and weak reaction was seen to CD117 and TdT (Figure 7). These microscopic features along with immunohistochemical studies confirmed the diagnosis of Granulocytic sarcoma. The same along with haematological findings was considered as relapse of AML.

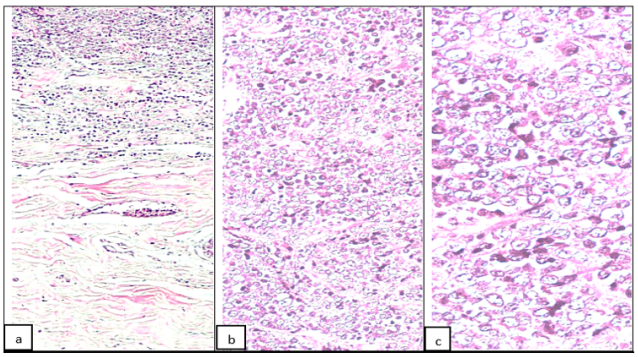

Fig. 5: H&E sections from the breast mass reveal a tumour composed of monomorphic population of cells, predominantly composed of blasts (**b,** 200x; **c,** 400x) along with a few mature and immature granulocytes. Normal breast parenchyma is seen at the periphery (**a,** 100x)

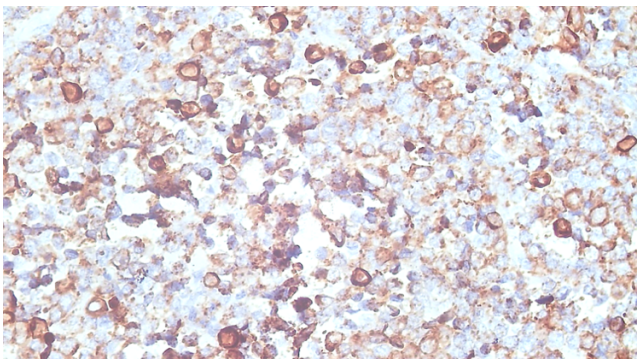

Fig. 6: Myeloperoxidase stain highlights the myeloid blasts in the breast mass. (400x)

She was started on FLAG-Ida (Fludarabine, Daunorubicin, Cytosar) regime of salvage chemotherapy along with administration of G-CSF. Post chemotherapy she developed pancytopenia with mucosal bleeds, for which she received PRBCs and SDP. Her overall general condition gradually improved and was declared fit for discharge with a monthly follow-up.

3. Discussion

Granulocytic sarcoma, also known as myeloid sarcoma or chloroma is defined as a tumoral mass which is formed by immature myeloid cells in the extramedullary area.[1] They are uncommon extramedullary tumours composed of malignant myeloid precursor cells and are mainly associated with AML. They are seen in 1-5% of AML cases. Uncommonly, they can also be associated with other myeloid malignancies and myelodysplastic syndromes. They may also arise de novo with no past or concurrent history of AML. In literature, GS is known by many other names, such as monocytic sarcoma, extramedullary myeloid cell tumour, extramedullary leukaemia and myeloblastoma. Historically, the term "Chloroma" was coined because of their greenish colour (Chloros = Green in Greek), which is due to their high MPO content. Burns described the first case of Granulocytic Sarcoma (GS) and called it Chloroma in 1823, while the first case of AML associated GS was reported in 1903 by Turk, who suggested the same origin for both of the tumours.[2] Subsequent studies also confirmed this strong association of GS with AML. Therefore, GS forms an essential subgroup of myeloid neoplasia and AML in the WHO classification of tumours of haematolymphoid malignancies

GS has a slight predilection for males (Male: Female ratio = 2:1). In the report of Ohanian et al.,[3] GS was seen in 9% of all age groups of AML. However, GS affects more commonly children than adults and 60% patients are younger than 15 years of age.[4] It has been mainly reported in North America, Europe, East Asia and South Asia. Although it can occur in any part of the human body, the most common anatomic sites of occurrence of GS include the periosteal bones of the skull, paranasal sinuses, sternum, ribs, vertebrae, lymph nodes, soft tissue and skin. Other common sites include the ovary, uterus and the epidural region. Less commonly, it may also involve the orbit, intestine and mediastinum. Breast involvement by the tumour is relatively rare. A historical retrospective study in patients with AML from Hiroshima and Nagasaki has described the involvement of breast in approximately 8% of cases.[5]

GS is relatively more common in patients with AML with prominent monocytic differentiation, mainly myelomonocytic (AML-M4 according to the French-American-British-FAB classification) and monocytic (AML-M5) leukaemia. However, as per Mustafa Cakan et al.,[1] GS may accompany AML M2 more commonly than other subgroups. Our patient was a diagnosed case of AML-M2.

Although the overall incidence of GS in AML has been reported at 1-5%, it is particularly high in some subtypes of AML, mainly AML with recurrent genetic abnormalities, reaching 18-24% in AML with t(8:21). Other genetic abnormalities diagnosed in GS patients include t(15:17), t(9:11), t(1:11), t(8:17), del(16q), del(5q), del(20q), monosomy 7, trisomy 4 and trisomy 8.[6]

The t(8:21) has been reported as the most common cytogenetic abnormality associated with GS, occurring both

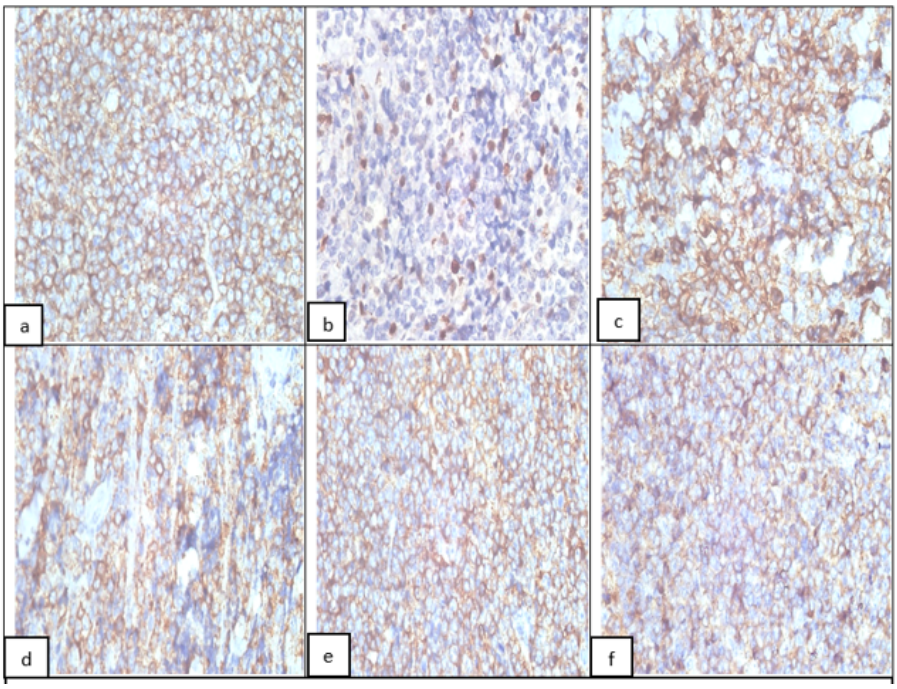

Fig. 7: Immunohistochemical profile of the breast lump (400x)- The tumour cells are strongly reactive for LCA **(a)**: TdT highlights the myeloblasts **(b):** CD43 **(c):** CD68 **(d):** CD117 **(e):** and CD99 **(f):** also react diffusely to the tumour cells

at presentation and upon relapse, and is associated with orbital involvement in infants. It is seen in approximately 18% of M2 AML. A critical event in the pathogenesis may be the formation of a novel chimeric gene and message as the result of the two genes' fusion – ETO from chromosome 8 and AML1 from chromosome 21.[7] The locations where GS develop in these cases seem to differ between adults and children. Although children with t(8;21) associated AML (under 15 years) commonly develop GS in the Head and neck (orbit or skull), GS in adults (over 15 years) have a tendency to form in the paraspinal area. Breast involvement by GS is more commonly associated with Inv (16). In addition, GS is frequently found at relapse in adults. Our patient, a 13-year-old female, with GS of the breast in relapse of AML with t(8;21), therefore makes for a relatively rare case, the peculiarity consisting the unusual site of localization of GS in an adolescent female, a case of AML with t(8;21).

According to the World Health Organization, granulocytic sarcomas can be classified into 3 categories: blastic (composed mainly of myeloblasts), immature (composed of myeloblast and promyelocytes), and differentiated (composed of promyelocytes and more mature neutrophils).[8] In our case, since majority of the cells composed of myeloblasts along with the presence of few immature cells, it can be classified into the blastic subcategory.

Clinically, granulocytic sarcoma of the breast presents with non-specific symptoms that are usually painless or painful palpable breast lumps involving one or both breasts. Breast skin involvement and axillary lymph node enlargement may accompany such cases, while nipple discharge and retraction are not commonly observed. Radiologically, breast GS typically presents as solitary or multiple masses that are mostly homogeneously hypoechoic with microlobulated or indistinct margins. It rarely presents as architectural distortions on sonography. Moreover, sonomammography is of limited use for evaluation of adolescent breasts due to the relatively higher ratio of fibroglandular to fatty tissue and sometimes even a clinically palpable mass may be missed by mammography.[9] This also could have been a reason for not carrying out sonomammography in our patient.

Due to the versatility of clinical presentation, diagnosis of GS can be missed or misdiagnosed in approximately half of the cases if histopathological examination and immunohistochemistry is not used. An IHC panel consisting of MPO, CD43, lysozyme and CD68 antigens are uniformly identified as the most sensitive markers of GS. Other commonly used myeloid markers include CD33 and CD117.[2] CD99 can also be used as a marker for GS. CD99 reactivity in GS has important clinical and diagnostic implications; as such tumours may be mistaken for other CD99 positive small round cell tumours, such as Ewing's/PNET group. Further, some recent reports have suggested the role of anti CD99 mAbs as novel therapeutic agents for CD 99 positive AML/GS. The theory postulated is that leukemic stem cells (LSCs) of AML

have the capacity to self-renew and differentiate into non-self-renewing progeny that comprise the vast majority of leukemic blasts. These LSCs are found to be resistant to conventional chemotherapy and are thought to serve as reservoirs of Minimal Residual Disease (MRD) causing disease relapse following initial chemotherapy. A study conducted by Chung et al.,[10] states that expression of CD99 allows for prospective separation of leukemic stem cells (LSCs) from functionally normal hematopoietic stem cells (HSCs) in AML. Monoclonal antibodies (mAbs) targeting CD99 induce the death of these AML cells in SRC family kinase dependent manner in the absence of immune effector cells or complement. Administration of anti CD99 mAbs has exhibited anti leukemic activity in such cases and hence can be used as potential therapeutic targets in AML. In our case, the tumour cells were diffusely positive for CD99.

Another marker that can be used as a prognostic indicator is CD56. CD56 is an adhesion molecule, normally expressed on NK cells. Expression of CD56 on leukemic cells is suggested to be associated with GS. Previous studies have reported that certain chromosomal abnormalities such as t(8;21), are often associated with CD56 expression, which increases the incidence of GS or its relapse following treatment.[6] Also, GS which express CD56 have a poorer prognosis. In our case, the cells of GS were diffusely reactive for anti CD56 antibody (Figure 8).

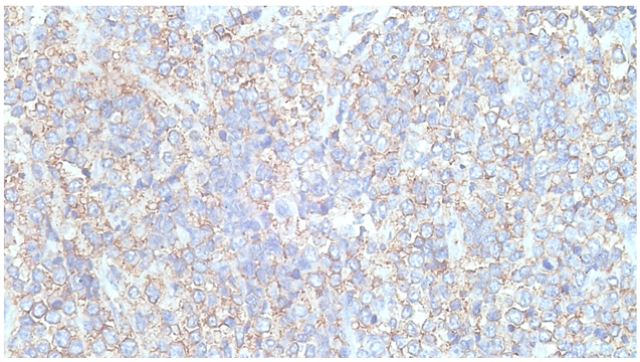

Fig. 8: The tumour cells show strong and diffuse reactivity for CD56 (400x)

Patients with GS are treated in the same way as patients with AML independently from bone marrow involvement. Infact, extra-medullary disease should be considered as a systemic disease and treated with a double therapeutic approach including systemic chemotherapy and additional intrathecal chemotherapy. Chemotherapy is considered the best therapeutic option, although our patient also underwent surgical excision of the mass for establishing a definitive diagnosis. Chemoradiation can also serve as a bridge to allogeneic stem cell transplant to prevent bone marrow relapse.

In conclusion, GS of the breast is an uncommon neoplasm associated with AML, less commonly associated with AML with t(8;21) and has an unfavourable prognosis. However, an early intervention along with timely diagnosis, including a complete staging of disease, an accurate molecular study, and a timely delivered chemoradiotherapy followed by allogeneic transplant procedure, is crucial to improve survival. Additionally, CD99 can also be used as a marker from a therapeutic point of view.

4. Source of Funding

None.

5. Conflicts of Interest

None.

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