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Case report

Radiotherapy for granulocytic sarcoma of the breast—Case report and review of the literature

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ABSTRACT

Granulocytic sarcomas are rare tumors that can present in innumerous locations; thus there is very little clinical experience with these cases. Therefore there is no consensus on which is the best treatment for patients with this malignancy.

The authors present a case of a female with a granulocytic sarcoma of the breast and review the literature for the role of radiotherapy in the management of this clinical entity.

1. Introduction

Granulocytic sarcomas (GS) are rare manifestations of acute myeloid leukemia (AML). They consist of immature myeloid cells that proliferate producing a clinically evident tumor.[1,2] These normally occur associated with AML, nevertheless very rarely they might present as isolated malignancies.[1,3]

Isolated GS of the breast (i.e. without medullary evidence of leukemia) are somewhat rare, and frequently associated with a dismal prognosis prompting treatment optimization.[3–5]

In the following section a case of an isolated GS of the breast is presented.

2. Case report

Thirty-five years old female with no relevant medical history, on auto-examination of the breasts found a tender nodule on the left breast.

Physical examination revealed a 25 mm nodule on the upper external quadrant of the left breast, without any other relevant findings.

The patient was submitted to an ultrasonography and a mammography. These showed a solid heterogeneous nodule, measuring 19.5 mm × 22 mm × 21 mm on the upper external quadrant of the left breast and a small lymph node on the ipsilateral axilla.

A tru-cut biopsy of this lesion was performed. Pathological analysis was inconclusive; however GS and myofibroblastoma were referred as the most likely diagnoses; lymphoma, carcinoma and melanoma were excluded.

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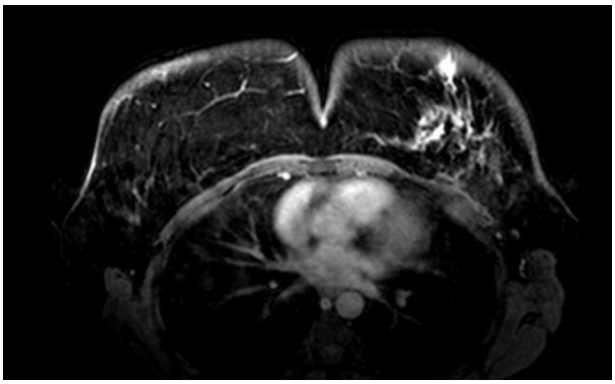

Fig. 1 – Post induction chemotherapy MRI.

Therefore the patient underwent tumorectomy. The final histologic diagnosis was GS with the following immunophenotype: myeloperoxidase+ CD45+, CD68+, CD34+, CD31+, CD43+, Cam 5.2−, CD117−, CD3−, CD20−, TdT−, CD10−.

As part of the workup a bone marrow study was conducted, it revealed a normocellular marrow with no excess of immature cells, some atypia and signs of dysmyelopoiesis.

The patient underwent chemotherapy treatment: induction with idarrubicin and cytarabine, followed by consolidation with 4 cycles of cytarabine. There were complications during the consolidation phase: febrile neutropenia, pulmonary aspergillosis, pyelonephritis and severe enterocolitis (with need for parenteral nutrition).

A post induction chemotherapy magnetic resonance (MRI) showed persistent disease (Fig. 1)

Another MRI, performed after completion of the entire chemotherapy regime, revealed a heterogeneous enhancement with approximately 60 mm (Fig. 2)

On a follow-up MRI, 3 months post chemotherapy, there was no evidence of disease.

After resolution of the adverse reactions, the patient underwent radiotherapy (RT). Radiation was delivered to the left breast with a 3D conformal (multi-leaf collimator) technique: 30 Gy in 2 Gy fractions (1 fraction per day, 5 days per week), with 6 MV photons, in a total of 21 days (Fig. 3). There were no interruptions of the treatment or any severe reactions. By the end of the treatment the patient had grade 2 dermatitis of the breast skin (CTCAE v4.03).

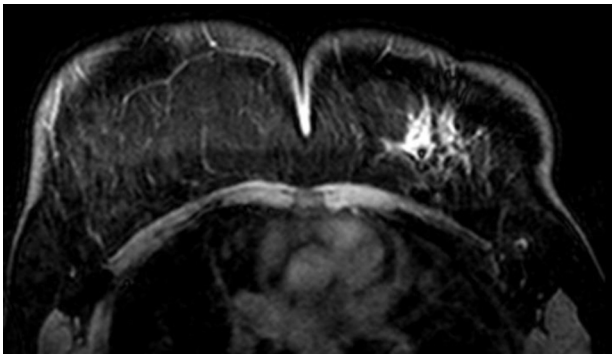

Fig. 2 – Post chemotherapy MRI.

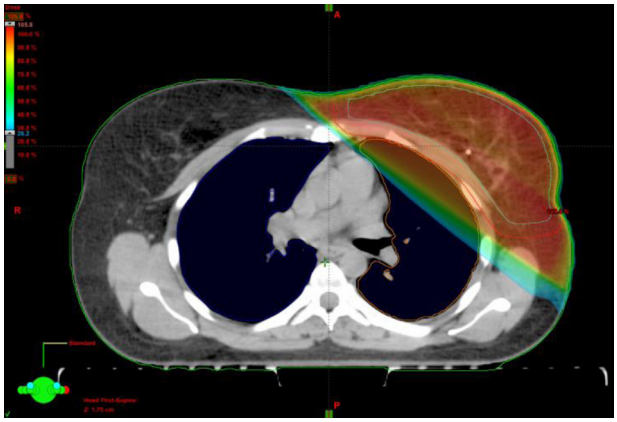

Fig. 3 – RT dose distribution (color wash).

At 26 months follow-up the patient remains asymptomatic and there is no evidence of relapse of the disease.

3. Discussion

Granulocytic sarcomas, or chloromas, are rare solid tumors, composed of immature myeloid cells, which occur in extramedullary locations.[1,2] This malignancy was first described by Allan Burns in 1811.[6] It was not until 1853 that the term chloroma was coined by King A.[7]; it derives from the Greek *chloros*, meaning green, due to a green tint that myeloperoxidase gives these cells. However, the presence, concentration, and oxidative status of this enzyme vary among tumors, giving cells different colors, 30% are white, grey or brown. Therefore the term Granulocytic Sarcoma, introduced by Rappaport in 1966[8] is nowadays the most used one. This initially referred only to tumors of granulocytic origin, as GS most frequently develop in patients with AML.[1,3] This association was firstly noted by Dock and Warthin in 1902.[9] Nevertheless, it can also be associated with chronic myeloid leukemia, myelodysplastic syndrome, chronic idiopathic myelofibrosis, hypereosinophilic syndrome and polycythemia vera hence the current broader use of the term granulocytic sarcoma.[1,3,4,10,11] These tumors present more frequently concomitantly or after the diagnosis of AML, there are, however, some cases where GS antedates AML.[1–5,10–13]

Some have argued that there is a slight male predominance, however many series fail to show any difference in gender.[1–4,10,11] Age of incidence ranges from 2 to 81 years (mean 33–48 years) depending on the series.[1–3] In a large autopsy series published by Liu et al. that comprised 338 cases of myeloid leukemia (both acute and chronic) of which 23 had GS, age at onset was the only factor with statistical significance, with younger patients having a higher risk of developing GS (under 15 years-old 13.6%; 15–44 y 6.7%; 45–59 y 4.4%; 60 y 0%).[11]

Granulocytic sarcomas can virtually occur anywhere in the body, however it more frequently arises in the skin, subperiosteal bone (cranium, paranasal sinuses, sternum, ribs, and vertebrae), soft tissues of the head and neck, orbit, central nervous system and lymph nodes.[1–4,10,11,13,14] The breast

is a relatively rare site for this malignancy, with few cases reported, due to its rarity it is often misdiagnosed as fibroadenoma, lymphoma, carcinoma and sarcoma.[1,3,14,15]

Diagnosis requires finding myeloid cells in the lesions. Morphologic characteristics can vary depending on maturation degree (mature, immature or blastic) and special dyes might be necessary to make the diagnosis. Many features can aid in confirming the diagnosis, such as: positivity for chloro-acetate esterase, myeloperoxidase, CD34, CD43, CD117 and CD68.[2,14] Several genetic anomalies have been associated with GS, such as t(8;21) and inv(16), these result in AML1/ETO (RUNX1/RUNX1T1) and CBFβ/MYH11 gene fusions respectively.[4,16,17]

Clinically GS of the breast may present as a unilateral or bilateral mass, usually without associated signs or symptoms such as retraction of the skin or mammillary discharge.[15,18,19]

Mammography and ultrasonography are unspecific exams. In mammograms lesions can be well circumscribed as well as irregular and infiltrative.[20–23] This is also noted on ultrasonography, where lesions are usually hypoechoic.[20,23] In computed tomography GS appear isodense to muscle.[21] In MRI lesions are heterogeneous, hyperintense in T2, with homogeneous enhancement with contrast.[23,24] MRI can be useful in evaluating response to chemotherapy, detecting residual disease or clinically undetectable relapses, which might allow for an earlier start of treatment.[24]

Treatment modalities include surgical excision, RT and chemotherapy.[2,3,10,17] Despite systemic treatment usually being effective, RT has been gaining more importance in the management of this disease. There has even been a reported case of a complete response of a breast GS (in a post AML setting) treated exclusively with RT (with a dose of 24 Gy).[22]

In circumstances where GS, due to its localization, demands a rapid symptomatic relief, or decompression of a vital structure, RT or surgery should be done prior to chemotherapy. However, there is no evidence that combined therapy is superior to isolated chemotherapy.

Treatment recommendations are highly dependent on response to chemotherapy and whether GS was an initial diagnosis or if it developed in a relapse setting. Ideal timing and treatment are still a dilemma.

Many authors argue that RT is associated with a longer disease free survival, others consider that it should be used as a consolidation treatment in isolated GS, especially since the effective dose is quite small. The area to be irradiated and associated toxicities are important factors to consider.[13] RT must always be considered when there is an incomplete response to chemotherapy. As a palliative treatment option it has excellent results in symptomatic relief.[13]

Granulocytic sarcoma is a radiation sensitive malignancy, i.e. responds to low doses.

In a study by Chak and colleagues, that analyzed palliative RT treatments to symptomatic lesions, it was reported that response to treatment was directly related to total dose, with calculated chances of complete response of 18 ± 9% for less than 10 Gy, 43 ± 11% for 10–19.99 Gy, 86 ± 14% for 20–29 Gy and 89 ± 10% for more than 30 Gy.[25] This led to a recommendation of at least 30 Gy in 15 fractions over 3 weeks, when chemotherapy is not effective.[25]

More recently Bakst et al.[13] have argued that the minimum dose could be as low as 20 Gy and propose a 24 Gy in 12 fractions treatment, which they report as effective and safe. They have also suggested that target volume should include residual disease post chemotherapy with a 10–20 mm margin and that treatment could be delivered with photons or electrons (for superficial lesions).[13]

However, doses ranging from 4 to 40 Gy have been reported. Song et al.[10] propose doses according to tumor size: more than 25 Gy (or BED_{10} 30 Gy) if the tumor is less than 10 cm^2; a larger dose if >6 cm or 30 cm^2 or if the tumor is not located in soft tissue. In palliative treatments a dose of at least 20 Gy is suggested.[10]

Despite the fact that the benefit of RT in global survival is yet to be proven, this treatment can contribute to increase disease free survival in isolated GS cases, especially those that have a partial response to chemotherapy.[13]

There might be occasional long survivors; however prognosis is usually reserved.[3,4] In a large series of 92 patients, 89.5% of patients had died from the disease at a median follow-up of 150 months.[4] Relapses are more often in the first two years, therefore during this period a tight surveillance is recommended. Long-term follow-up has shown that patients who achieve complete response have long remission free periods, and in some cases can potentially achieve cure.

4. Conclusion

Granulocytic sarcoma of the breast is very rare and, like the case presented, many patients do not have systemic signs of the malignancy. Imaging gives little help in distinguishing GS from carcinoma or lymphoma. Histology plays a major role in the diagnosis, but can sometimes be inconclusive, especially in poorly differentiated tumors that mimic other neoplasms.

It has been argued that RT might increase disease or progression free survivals, however this remains unproven. Radiotherapy can be considered essential when GS presents isolated, when there is a partial response to chemotherapy, when there is a relapse after allergenic transplant or as a palliative treatment to rapidly relief symptoms. The proposed dose ranges from 20 to 30 Gy, using a conventional fractionation (2 Gy per fraction), which, in most cases, achieves disease control with minimum morbidity.

Conflict of interest

None declared.

Financial disclosure

None declared.

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