

Dedifferentiated liposarcoma presenting with unexplained leukocytosis

Carla M. Martín-Abreu¹, Ana Godoy-Reyes¹, Fernando Armas-González¹, Onán Pérez-Hernández¹, Carmen Nieves Hernández-León², Beatriz Esquivel-Vázquez³, Cristina Vila-Zarate⁴, Emilio González-Reimers¹.

¹ Servicio de Medicina Interna. Hospital Universitario de Canarias. Universidad de La Laguna

² Servicio de Anatomía Patológica. Hospital Universitario de Canarias. Universidad de La Laguna

³ Departamento de citogenética. Hospital Universitario de Canarias. Universidad de La Laguna

⁴ Servicio de Cirugía General y Digestiva. Hospital Universitario de Canarias. Universidad de La Laguna

*Correspondence: Carla M. Martín-Abreu carla.martin.abreu@gmail.com

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Summary

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Introduction: Liposarcoma usually presents as an asymptomatic incidental tumor or with symptoms associated with the mass effect. Manifestations related to the inflammatory response against the neoplastic disease are uncommon, especially in early stages, and paraneoplastic features, including leukocytosis, are exceptional.

Case report: We present the case of a patient who developed progressive leukocytosis that first appeared three months before admission. A mass was discovered both by computerized tomography and magnetic resonance, and after a non-conclusive first biopsy, in which intense neutrophilic infiltration suggested a pyomyositis, a dedifferentiated liposarcoma was identified when the tumor was excised. Leukocytosis, that reached 41.52x10⁹/L two days before surgery, abated to 12.13x10⁹/L.

Discussion: In a review of 2007 only 6 cases of liposarcoma with leukocytosis had been described, and only a few cases have been reported afterwards. We hypothesises about the relation between this leukocytosis and the liposarcoma.

Keywords: G-CSF. Leukocytosis. Liposarcoma. MDM2. Paraneoplastic manifestations. Psoas mass.

Resumen

Liposarcoma diferenciado que se presenta con leucocitosis no explicada.

Introducción: Los liposarcomas se suelen presentar como hallazgos incidentales asintomáticos o con síntomas asociados al efecto

masa. Las manifestaciones clínicas relacionadas con el desarrollo de una respuesta inflamatoria contra el tumor y las manifestaciones paraneoplásicas, incluida la leucocitosis, son excepcionales.

Caso clínico: Presentamos el caso de un paciente con una leucocitosis progresiva que comenzó tres meses antes del ingreso. En diferentes pruebas de imagen (tomografía computarizada y resonancia magnética) se objetivó una masa en el psoas derecho que tras una primera biopsia con resultado anatomopatológico de infiltrado neutrofílico altamente sugestivo de piomiositis, requirió una biopsia excisional para su diagnóstico definitivo, en este caso, un liposarcoma dediferenciado. La leucocitosis que alcanzó valores de 41.52x10⁹/L, dos días después de la cirugía descendió hasta 12.13x10⁹/L.

Discusión: En una revisión de 2007 solo se habían descrito 6 casos de liposarcoma con leucocitosis y solo unos pocos casos más han sido reportados hasta ahora. Nosotros estudiamos la relación entre la leucocitosis y el liposarcoma.

Palabras Clave: G-CSF. Leucocitosis. Liposarcoma. MDM2. Manifestaciones paraneoplásicas. Masa del psoas

Introduction

Liposarcoma is one of the most common soft tissue sarcoma and 50% of them are located in retroperitoneum, accounting for about 50% of all retroperitoneal sarcomas [6]. There are five different histological types (well differentiated, dedifferentiated, myxoid, round cell and pleomorphic), grouped in three families depending on common genetic alterations [1]. Most cases are asymptomatic and only a few

patients present symptoms related to mass effect. Both paraneoplastic manifestations and those derived from tumor-associated inflammatory response are extremely rare. Therefore the diagnosis is usually made after the incidental finding of a mass but very uncommonly by systemic manifestations. Among these,

leukocytosis is a rare finding that has been put in relation with increased production of G-CSF (granulocyte colony stimulating factor) [10]. We here present the case of a patient with a progressive leukocytosis that was serendipitously discovered in a routine analysis

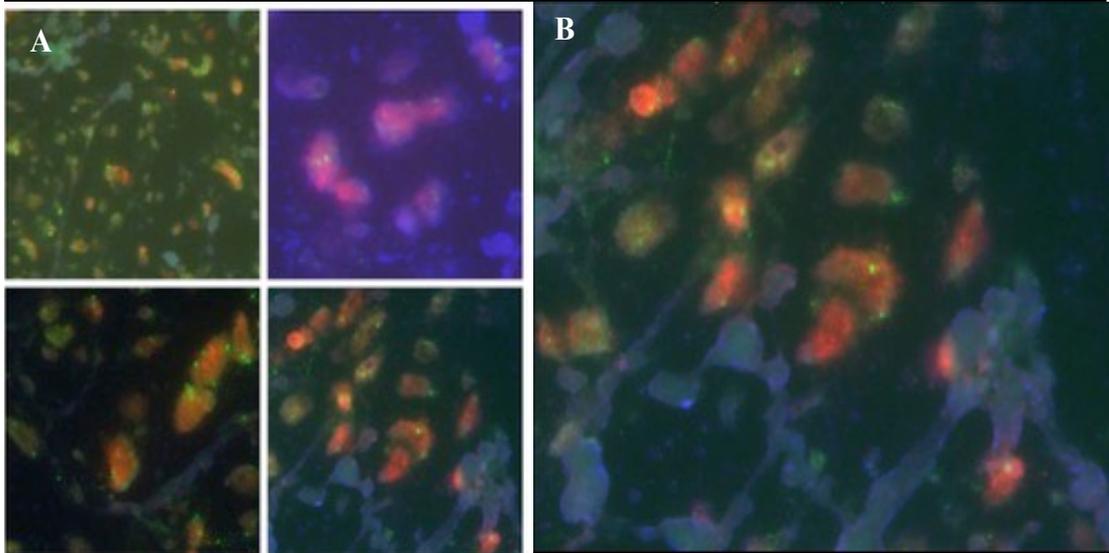


Figure 1: The sample was hybridated with DNA LSI MDM2 Spectrum Orange/ CEP12 Spectrum Green (Werfen Group) (A). In red colour (B) it is observed the 12q15 amplification which includes murine double minute 2 gene (MDM2). In green colour the hybridation signals of chromosome 12 centromere

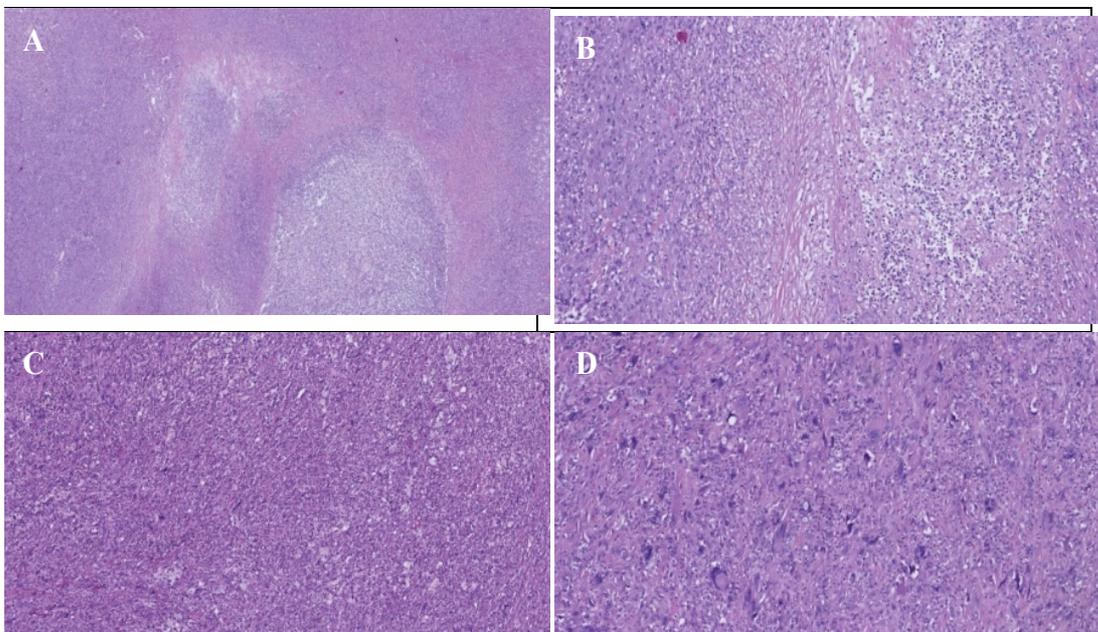


Figure 2: (A) Tumor with abscessed area. HE 40X. (B) A transitional zone between abscess and tumor. HE 100X (C) Tumoral cells in an acute inflammatory background. HE 100X (D) Tumoral pleomorphic cells, atypical cells and lipoblasts. HE 200X

CASE REPORT

A 65-year old man was referred to our hospital with a progressive leukocytosis that was confirmed three times before admission, without any other complaint. Once a myeloproliferative syndrome was excluded (negative results regarding BCR/ABL and JAK 2) we requested an abdominal ultrasound scan in which a retroperitoneal mass in the vicinity of the right kidney was observed. An abdominal computerized tomography (CT) was performed, showing a mass on the right psoas. A magnetic resonance (MR) was informed as a possible sarcoma with a small, nearby located nonspecific lesion in the right renal hilum. After directed anamnesis the patient denied hematuria and he only reported a vague sporadic discomfort in the right lower part of the abdomen together with occasional asthenia and subtle malaise. During admission leukocytosis continued increasing ($34.30 \times 10^9/L$, $30.90 \times 10^9/L$, $28.94 \times 10^9/L$, $34.94 \times 10^9/L$). In view of the findings of CT and MR we decided to perform a CT-guided needle biopsy. The pathological result was an inflammatory infiltrate without malignant cells. Given these findings, we interpreted that the patient suffered a pyomyositis so he was treated with ceftriaxone and tigecycline. Despite this treatment, the leukocytosis raised up ($41.52 \times 10^9/L$). An excisional biopsy was therefore performed and the whole lesion was histologically analyzed. The anatomopathological diagnosis was dedifferentiated liposarcoma. In an analysis performed the following day after surgery leukocyte count abated to $12.13 \times 10^9/L$ and one month later it counts $6.6 \times 10^9/L$.

Discussion

We have reported the case of a patient undoubtedly affected by a dedifferentiated retroperitoneal liposarcoma. There are five histological types of liposarcoma grouped in three families depending on shared genetic alterations: pleomorphic liposarcoma usually lacks the tumor suppressors genes p53 and Rb; myxoid and round cells liposarcoma carries a translocation of FUS and DDIT3 genes [3]; well differentiated and dedifferentiated liposarcoma join the 12q13-15 amplification, related to MDM2, CDK4 and HMGA2 oncogenes, so both are grouped in the same family. Co-amplification of MDM2 and CDK4 is a common feature [9]. In the present case, the final histological diagnosis was a dedifferentiated liposarcoma with MDM2 positive mutation shown by fluorescence in situ hybridization (FISH) (Fig 1) Retroperitoneal liposarcoma usually behave as highly malignant tumors, with a great rate of

recurrence [19]. Treatment options include local excision. However, the optimal resection extent is controversial. In some sarcoma centers adjacent organs or structures are removed, even without evidence of tumor invasion [11] Radiotherapy could be administrated intraoperatively and/or as an adjuvant treatment [20]. With this approach, 3-year overall survival may reach 82% [7]. Standard chemotherapy includes the use of anthracycline (doxorubicin) or anthracycline-based combinations (doxorubicin with ifosfamide or dacarbazine). Second line combinations frequently are based on non-anthracycline combinations as gemcitabine and docetaxel [21]. Recently, cyclin-dependent kinase inhibitors may offer some promise [16]. Dedifferentiated liposarcomas are relatively chemoresistant, so systemic therapies are rarely useful. Nevertheless, the recent discovery of specific mutation opens the door to targeted treatments. MDM2 antagonists (RG7112) restored p53 activity to induce cell cycle arrest and apoptosis, avoiding tumor perpetuation [14] There is a phase 2 trial with Palbociclib aCDK4 inhibitor. The inactivation of CDK4 would restore normal cell cycle and avoid uncontrolled tumor proliferation [2].

The case here reported presents some unusual features. At first, it constitutes a new example of the uncommon occurrence of leukemoid reaction associated with liposarcoma. To our knowledge, after a throughout literature review, we have only found around 10 cases of liposarcoma with leukocytosis, a review of 6 cases 10 years ago [15] and isolated cases until our days [4, 5, 18]. In this case, the presence of progressive leukocytosis allowed the diagnosis of the tumor because otherwise that patient was fully asymptomatic. In the few cases reported as yet, G-CSF was determined only in four of them [5, 10, 15, 17]. A marked increase of this parameter was detected in all these cases, that returned to normal values after tumor excision.

A striking feature of the histological picture was an intense neutrophilic infiltrate, that lead to the misdiagnosis of an infectious process in the first CT directed needle biopsy. Although speculative, it is possible that this intense acute inflammatory infiltrate may reflect the secretion of G-CSF by the tumour cells. It has been shown that G-CSF not only promotes myelopoiesis, but also enhances granulocyte functions [13] and transmigration [22]. The result of this first biopsy also constitutes an important advice regarding the clinical approach to a patient with a retroperitoneal mass. A needle biopsy may be confusing in such situations since muscle associated masses may be due to pyomyositis.

This happened in our case. Fortunately, the lack of normalization of the leukocyte count after intensive broad spectrum antibiotic therapy prompted us to perform a second biopsy, in this case an excisional one, that allowed the obtention of the correct diagnosis without having lost much time treating the patient with unnecessary antibiotics. (Fig 2)

One of the prognostic factors associated with better survival among retroperitoneal liposarcomas is tumor size [12], and one of the most important prognostic factors is complete resection and prompt treatment of local recurrence and/or metastatic lesions [8], something that may require close clinical follow-up and repeated total body CT and/or magnetic resonance procedures, since, as commented, paraneoplastic manifestations of retroperitoneal sarcomas are uncommon. In this sense, the uncommon leukocytosis presented by this patient may constitute in a certain way a clinical advantage, especially if it obeys to ectopic production of G-CSF. It is tempting to speculate that perhaps G-CSF and/or leukocytosis may behave in these patients in a way similar as PSA behaves in prostatic cancer. Future research in this field is urgently needed.

Conclusion

Paraneoplastic leukocytosis due to ectopic G-CSF production is a rare manifestation of retroperitoneal liposarcoma. We here reported the case of a patient in whom a dedifferentiated liposarcoma was serendipitously discovered during the evaluation of unexplained leukocytosis that appeared three months before the diagnosis. Leucocytosis increased until $41.52 \times 10^9/L$ and returned to normal values after tumor excision.

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