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CASE REPORT

Paraneoplastic Syndrome Associated with the Retroperitoneal Dedifferentiated Liposarcoma: an Atypical Presentation and Review of the Literature

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Abstract
Retroperitoneal liposarcoma is usually asymptomatic until it is large enough to compress the surrounding organs. Here, we report a rare atypical case of primary retroperitoneal dedifferentiated liposarcoma who presented primarily with the misguiding and challenging paraneoplastic symptoms of high-grade fever and thrombocytosis instead of demonstrating the usual compressive symptoms. Such an extremely rare clinical presentation may mislead the diagnostic and treatment approach towards the search for medical causes, without a hint, that the tumor itself is causing these symptoms. Complete tumor excision usually leads to resolution of these paraneoplastic symptoms.

Keywords Paraneoplastic syndrome · Dedifferentiated liposarcoma · Retroperitoneum · Fever · Thrombocytosis

Introduction

The paraneoplastic syndrome refers to a clinical condition that results from the systemic effects of the tumor and occurs distant from the site of primary tumor or metastasis. While the paraneoplastic symptoms are commonly seen in lung cancer, lymphoproliferative disorders, thymoma, gynecological, and renal malignancies, they are rarely associated with soft tissue sarcomas [1]. Neoplastic fever is defined as the fever resulting from the malignancy itself. Although it is one among the other causes of pyrexia of unknown origin (PUO) in cancer patients, still it is a diagnosis of exclusion [2]. Malignant solid tumors can also cause paraneoplastic thrombocytosis (defined as platelet count $>450\times10^3/\mu L$), which in turn promotes tumor growth and metastases, thus creating positive feedback loop [3]. Retroperitoneal liposarcoma is usually asymptomatic until it is large enough to compress the surrounding organs. Here, we report a rare atypical case of retroperitoneal dedifferentiated liposarcoma (DDLS) who presented primarily with the misleading and challenging paraneoplastic symptoms of high-grade fever and thrombocytosis instead of demonstrating the usual compressive symptoms.

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Case Report

A 48-year-old woman presented with the complaints of fever and generalized weakness for 1 month. Fever was of low grade and self-resolving nature initially for 1 week but gradually progressed to high-grade nature, requiring medical management. There was an associated history of significant weight loss. There was no family history of

any malignancy. On initial evaluation with ultrasound elsewhere, she was diagnosed with an abdominal lump, following which she was referred to us for further evaluation and management.

Clinically, pallor was visualized, and a palpable finding of a non-tender, firm to hard, ill-defined mass of size ~ 20 cm × 10 cm in her left lumber and the iliac region was demonstrable. There were no palpable lymph nodes. Her hemogram revealed features of microcytic hypochromic anemia (hemoglobin of 7.3 g/dL) and thrombocytosis (platelet counts 743,000/μL) with normal total leukocyte count. A contrast-enhanced CT of thorax and abdomen revealed a large heterogeneous mass with areas of visible fat and cystic areas with enhancing solid components in left retroperitoneum extending from left subdiaphragmatic region to left pelvis involving left adnexa and encasing left kidney (Fig. 1). She was running with high-grade fever, during the preoperative work up in the absence of neutropenia or leukocytosis. An extensive diagnostic workup for the cause of fever involving tests for dengue, malaria, typhoid, tuberculosis, brucellosis, and Epstein Barr virus was performed, and all these tests were found to be negative. Her blood and urine cultures were also negative, JAK2 V617 mutation and Exon 12 mutation tests were negative for essential thrombocytosis. After thorough workup and joint discussion in multidisciplinary tumor board, she was planned for surgical resection. Her hemoglobin level fell to 6.3 g/dL just before the surgery. She needed a preoperative blood transfusion, but it was challenging to find an afebrile window for blood transfusion.

Finally, she underwent radical resection of the retroperitoneal tumor along with the left nephrectomy and left salpingo-oophorectomy (Fig. 2). No new episodes of fever dramatically characterized the immediate postoperative period. Her platelet counts also returned to normal within 1 month. Histopathological examination of the resected specimen revealed a tumor consisting of adipocytic cells separated by thin to thick fibrovascular septa with focal areas of myxoid changes. There was an abrupt transition within the tumor, wherein, the tumor composed of highly cellular sheets and vague fascicles of markedly pleomorphic cells with giant tumor cells, and high mitotic rate including atypical forms. These findings were consistent with the diagnosis of a high-grade dedifferentiated liposarcoma (Fig. 3). She has no evidence of disease recurrence at 1.5 years of follow-up.

Discussion

Soft tissue sarcomas (STS) are among the rare neoplasms accounting for approximately 1% of all neoplasms [4]. In the recent 2013 update of WHO classification of STS, based on the histology and biological behavior, liposarcomas were subclassified into five subtypes: (a) well-differentiated liposarcoma, (b) dedifferentiated liposarcoma, (c) myxoid liposarcoma, (d) pleomorphic liposarcoma, and (e) liposarcoma, NOS [5]. DDLS is referred to a condition when WDLS shows the abrupt transition to a region of nonlipogenic sarcoma at least several millimeters in diameter. Radiologic

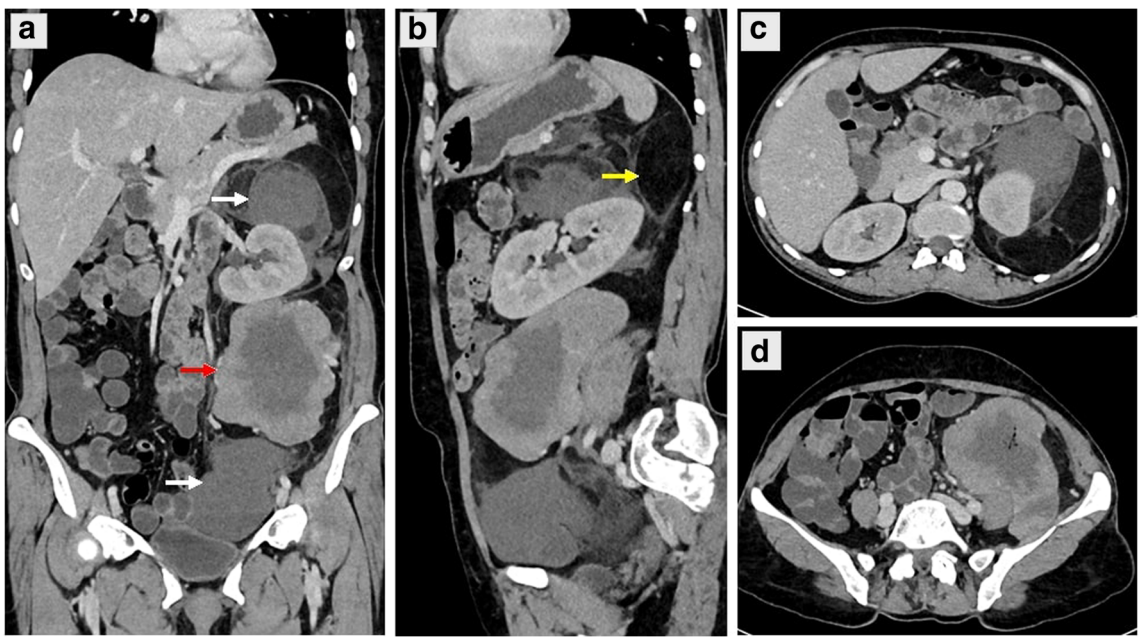

Fig. 1 Coronal section showing a large heterogeneous mass on the left side of retroperitoneum, extending from left subdiaphragmatic region to pelvis with areas of enhancing solid components (white arrows) and a large enhancing solid component with internal necrosis (red arrow), indicating the dedifferentiated areas **a**. The sagittal section is showing that the mass is encasing the left kidney. The yellow area points to the macroscopic fat component (the well-differentiated component) **b**. Axial views **c**, **d**

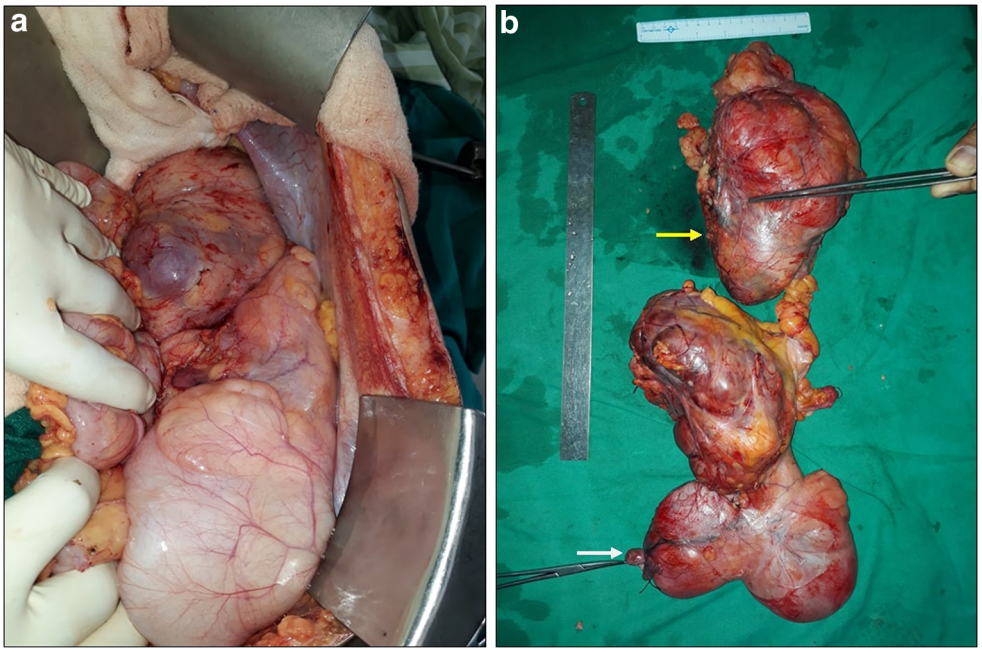

Fig. 2 Intraoperative photograph of the tumor **a**. Photograph of the resected specimen showing tumor encasing the left kidney (yellow arrow) and the left adnexa (white arrow) **b**

imaging typically shows coexistence of fatty and nonfatty solid components, which in the retroperitoneum may be discontinuous. Macroscopically, DDLS consists of large multinodular yellow masses containing distinct nonlipomatous (dedifferentiated) areas, which are solid and often tan to gray [6]. DDLS usually presents in late adult life without any gender predilection. We performed an extensive search of the literature for a paraneoplastic syndrome associated with DDLS and summarized in Table 1 [7–22].

In most of these cases, these unusual presentations resolved with complete excision of the tumor. The case reported in this article also bore the façade of an atypical presentation with fever and thrombocytosis, which led us to evaluate for other possible causes of these signs and symptoms. Finally, the

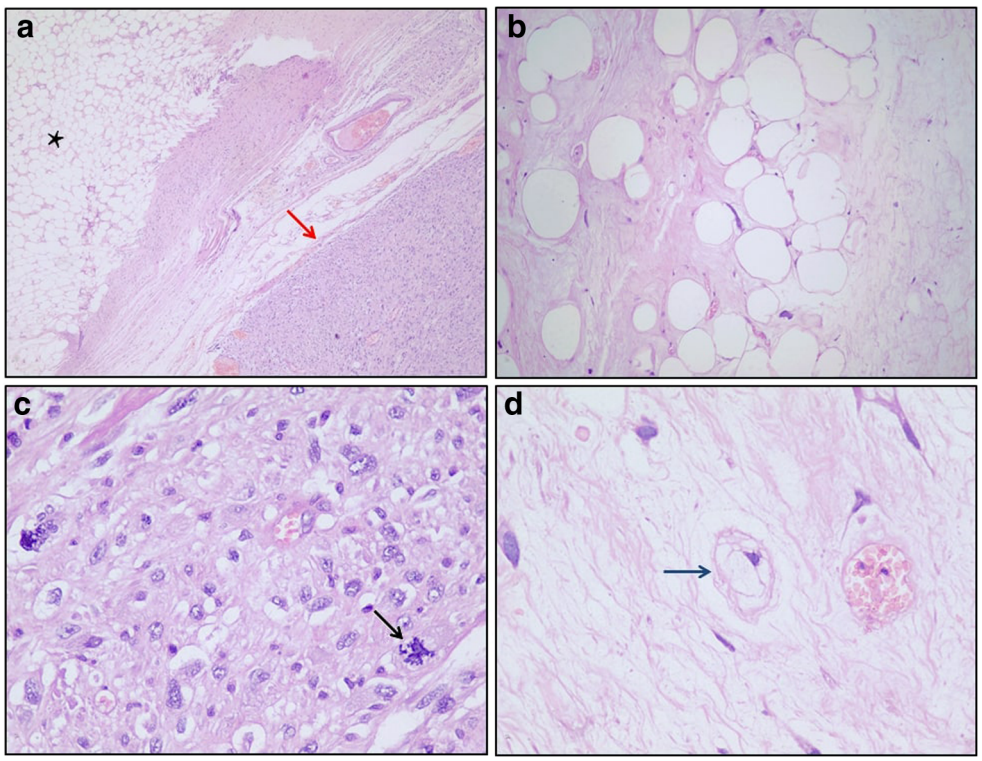

Fig. 3 Histopathological examination findings of the resected specimen. Scanner view is showing the abrupt transition of the typical adipocytic tumor (black asterisk) and high-grade tumor (red arrow) (H&E 4X) **a**. High power view of the tumor showing adipocytic cells separated by collagenous septae, and fibrillary background (H&E × 40) **b**. High power view from the high-grade tumor areas showing markedly pleomorphic and bizarre tumor cells with atypical mitotic figures (black arrow) (H&E × 40) **c**. The tumor is showing the presence of lipoblasts (blue arrow), with multivacuolated cytoplasm and hyperchromatic nucleus with scalloped margins (H&E × 40) **d**

Table 1 Reports of the paraneoplastic syndrome associated with the liposarcoma

S no.	Report	Paraneoplastic syndrome	Histological subtype	Resolution after complete tumor excision (yes/no)
1.	Parmeggiani et al. [7]	Hyperglycemia	Dedifferentiated	Yes
2.	Monma et al. [8]	Granulocyte colony-stimulating factor production	Dedifferentiated	Not known
3.	Maryamchik et al. [9]	β-HCG production	Dedifferentiated	Resection not performed
4.	Schöffski et al. [10]	β-HCG production	Dedifferentiated	Not performed
5.	Nasser et al. [11]	Leukemoid reaction	Dedifferentiated	Yes
6.	Tartaglia et al. [12]	Small plaque parapsoriasis	Undifferentiated	Yes
7.	Zhou et al. [13]	Cerebellar degeneration	Dedifferentiated	Yes
8.	Toyoda et al. [14]	Thrombocytopenia	Dedifferentiated	Yes
9.	Sherman et al. [15]	Glomerulopathy	Dedifferentiated	No
10.	Kondo et al. [16]	Retinopathy	Dedifferentiated	No
11.	Chan [17]	Subacute complete ophthalmoplegia	Myxoid	Yes
12.	Sator et al. [18]	Acrokeratosis paraneoplastica (Bazex's syndrome)	Dedifferentiated	Yes
13.	Bosco et al. [19]	α-fetoprotein production	Dedifferentiated	Yes
14.	des Guetz et al. [20]	Leukocytosis	Dedifferentiated	Yes
15.	Nakamura et al. [21]	Granulocyte colony-stimulating factor production	Pleomorphic	Yes
16.	Krunic et al. [22]	Lichen planus pemphigoids-like eruption	Round-cell	Yes
17.	Vishnoi et al. (Present case)	Fever and thrombocytosis	Dedifferentiated	Yes

confirmation that these features were in fact due to the DDLS was given by their abrupt resolution following the complete tumor excision. Here, we want to highlight the fact that the continuous high-grade fever, anemia, and thrombocytosis (these medical conditions) may render patient unfit for surgery and patient may lose the chance to get rid of the tumor as well as these associated symptoms.

Complete surgical excision without tumor rupture forms the mainstay in the management of resectable retroperitoneal WDLS and DDLS. Tumor invasion into adjacent organs or structures requires en bloc resection in order to achieve an R0 resection. The expertise of the treating center plays a very significant prognostic factor in terms of tumor recurrence and overall survival (OS). Outcome following local recurrence in both WDLS and DDLS is inferior, because, they usually tend to recur repeatedly despite re-resections, ultimately culminating in mortality [23]. In the past few years, extended liberal multi-visceral resection (en bloc resection of primary tumor and involved viscera along with resection of firmly adherent but uninvolved viscera) has demonstrated better local control rates and similar survival rates in comparison with traditional conservative resection [24–26].

Conclusion

Retroperitoneal DDLS presenting with atypical features of fever and thrombocytosis creates a diagnostic pitfall. Therefore, it is prudent to keep in mind that the atypical manifestations associated with the retroperitoneal liposarcoma, might be due to the mass itself instead of a second disease. A careful history might be able to provide certain clues to the association of the atypical presentation with the mass. Complete tumor excision usually leads to resolution of these paraneoplastic symptoms.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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