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CASE REPORT

Renal Ewing sarcoma with extensive neuroectodermal differentiation: Case report and literature review

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Ewing sarcoma with renal localization is one of the rarest members of the Ewing sarcoma family with less than 200 cases reported in the Medline database. Considering the fact that the majority of data published on the Ewing sarcoma with neuroectodermal differentiation is obtained through a few case reports and case series, it becomes understandable why we currently have no universally accepted treatment regimens. **Case summary**: A 33-year-old patient presented to the Emergency Department with right lumbar pain following a mild trauma and an episode of macroscopic hematuria. Physical examination confirmed hematuria and flank pain and a palpable flank mass was identified. MRI showed a cystic lesion of the upper pole of the right kidney of 127/110/123 mm. After prior agreement of the multidisciplinary team, a 3D laparoscopic right radical nephrectomy was done. The histopathological diagnosis revealed an Ewing sarcoma with extensive neuroectodermal differentiation staged as pT3N1M0L1V2R0. Despite swift implementation of the chemotherapy protocol, the progression of the disease was quickly noted. Currently, one year after diagnosis, the disease is still progressing despite the chemotherapy treatment, the patient being a third line chemotherapy candidate. As renal localization of Ewing sarcoma with extensive neuroectodermal differentiation is extremely rare, multimodal treatment strategies must be established by a multidisciplinary team. Despite its aggressive biological behavior, a proper therapeutic management might increase patient life expectancy.

Keywords: Ewing sarcoma, neuroectodermal, kidney, diagnosis, chemotherapy

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Introduction

The Ewing sarcoma (EWS) family includes several neoplastic entities such as EWS of bone, extraskeletal EWS, EWS with extensive neuroectodermal differentiation (formerly called primitive neuroectodermal tumor - PNET), EWS arising in the chest wall and paravertebral small-cell tumor [1,2].

EWS with extensive neuroectodermal differentiation was first described by Stout, as a PNET, in 1918, and was considered a variant of EWS, sharing the same pathologic features microscopically, immunohistochemically (IHC) and genetically [3,4]. It is described as a fast-growing small round cell tumor, which derives from the neural tube and shares ectodermal or neuronal differentiation abilities [5,6].

Renal localization of EWS with extensive neuroectodermal differentiation is extremely rare, most of our current knowledge deriving from case reports of tumors with aggressive biological behavior [5,7,8]. Less than 1% of renal tumors are EWS [5,7,8]. Most cases are metastatic at diagnosis or become metastatic after a few months [8]. Over 60% of patients show lymph node involvement but the pulmonary and bone metastases are the main cause of death [2,5,6].

Non-specific symptoms included in the "classic renal tumor triad" are hematuria, flank mass and flank pain [6]. The diagnosis is mainly established after the surgical removal of the tumor, based on IHC profile and cytogenetic studies [9,10]. Only in 24% of cases the complete surgical resection can be achieved [6,10,11]. Neoadjuvant and adjuvant chemotherapy show promising results in prolonging survival, but despite good initial response, local and metastatic recurrence are common features [1,6,10,11].

Less than 200 cases of renal EWS have been reported to date in the Medline database. In this paper, we present a supplementary case with renal localization, with extensive neuroectodermal differentiation, which was diagnosed in a very young patient. It showed a rapid progression of the disease despite the use of the two main chemotherapy regiment implemented. Thankfully, the clinical status of the patient remains satisfactory, thus he remains fit to continue the proposed chemotherapy treatment.

Case presentation

Personal history

A 33-year-old patient, with no medical history, was admitted to the Emergency Department complaining of right lumbar pain and an episode of macroscopic hematuria, therefore, a renal lithiasis was suspected. Physical exami-

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nation showed the classic renal tumor triad, respectively hematuria, flank pain, and a palpable flank mass.

Laboratory examinations

Hematological findings at diagnosis were normal despite the macroscopic hematuria, with hematocrit of 47.10% (normal range 40–54%) and hemoglobin of 16.30 g/dL (normal range 12–16 g/dL); no sign of infection was detected, leukocytes (8.10×10^3 cells/μL; normal range 4–10 $\times 10^3$ cells/μL) and neutrophiles (5.03×10^3 cells/μL; normal range 1.5–7 $\times 10^3$ cells/μL) were slightly increase, renal function at diagnosis was also normal with a creatinine serum level of 1.10 mg/dL (normal range 0-1.2 mg/dL).

Imaging

As the ultrasound examination emphasized a tumor mass, MRI was recommended. A cystic lesion of 127/110/123 mm (CC/LL/AP) proved to be located in the upper pole of the right kidney, with fine septa and several solid nodules adjacent to the wall, with contrast intake at their level. The peripheral nodules have a maximum size of 17/27 mm. The described lesions were classified as Bosniak category IV. No distant metastases were detected (Figure 1).

Surgery

After obtaining the signed informed consent of the patient, for surgical excision and publication of scientific data, a 3D laparoscopic right radical nephrectomy was performed through a transperitoneal approach. The postoperative MRI showed no sign of residual tumor mass but some lomboaortic, mesenteric, and interaortocave adenopathies with inflammatory morphology, the largest measuring up to 9 mm (Figure 2); the follow-up of the adenopathies was recommended.

Gross and histopathological assessment of surgical specimens

Macroscopically, the 130/160/90 mm tumor was encapsulated. On cut section, a cystic appearance with large areas of necrosis was described. The tumor mass did not exceed the capsule and did not infiltrate the pyelocaliceal system, but the renal vein was invaded.

Under microscope, a proliferation of round cells with scanty cytoplasm, scattered in perivascular sheaths, was characteristic (Figure 3).

Immunohistochemical and molecular profile of tumor cells

For further confirmation, IHC staining was performed. The tumor cells showed neuron specific enolase (NSE), GATA3 and diffuse membranous positivity for CD99, and did not express the leukocyte common antigen (LCA), CD20 or CD3 (Figure 3). Based on the histological findings and IHC profile, the diagnosis of renal EWS with

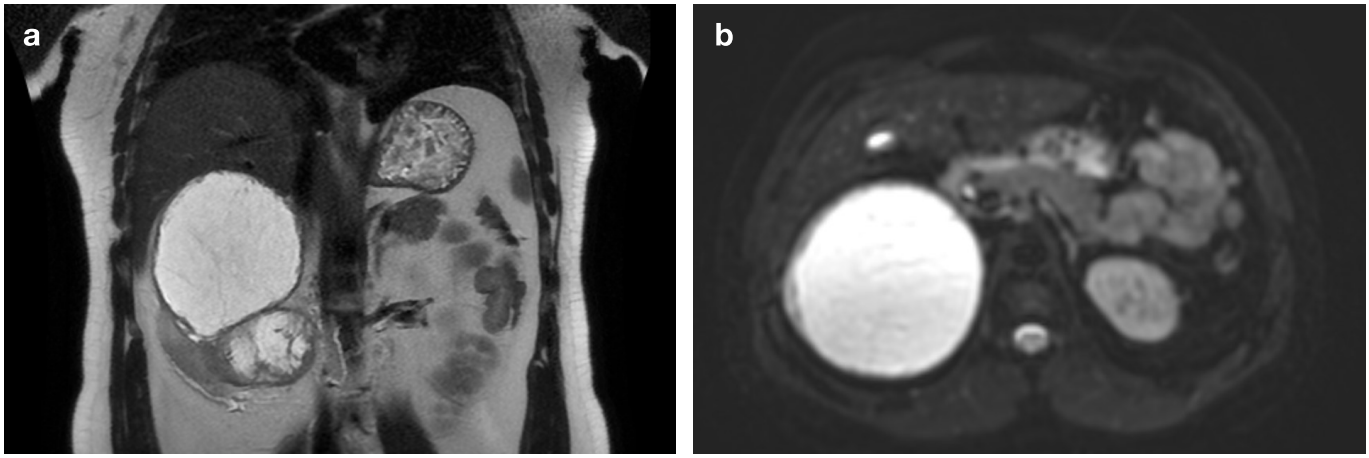

Fig. 1. Preoperative MRI imaging shows a cystic tumor of the upper pole of the right kidney: (a) Preoperative T2 coronal section. (b) Preoperative T2 axial section

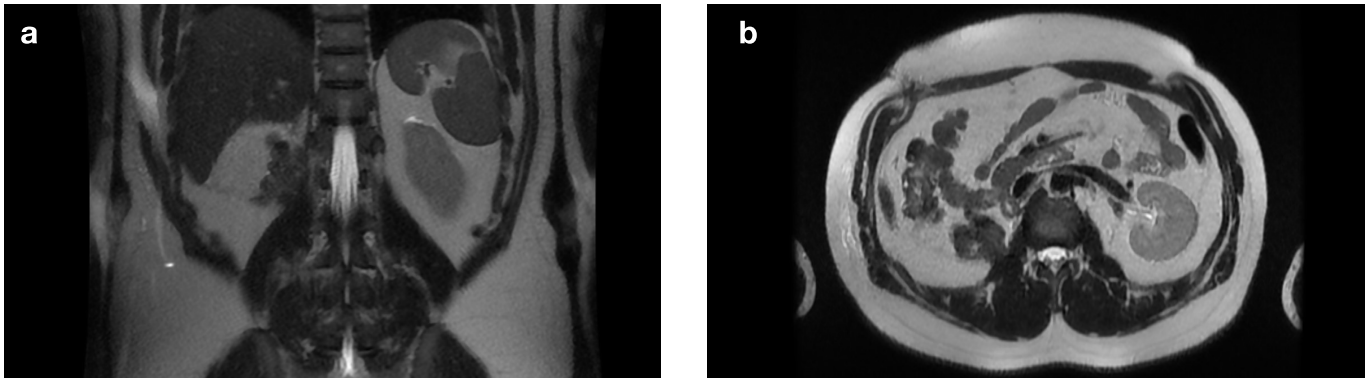

Fig. 2. Postoperative MRI imaging (a) Postoperative T2 coronal section (b) Postoperative T2 axial section

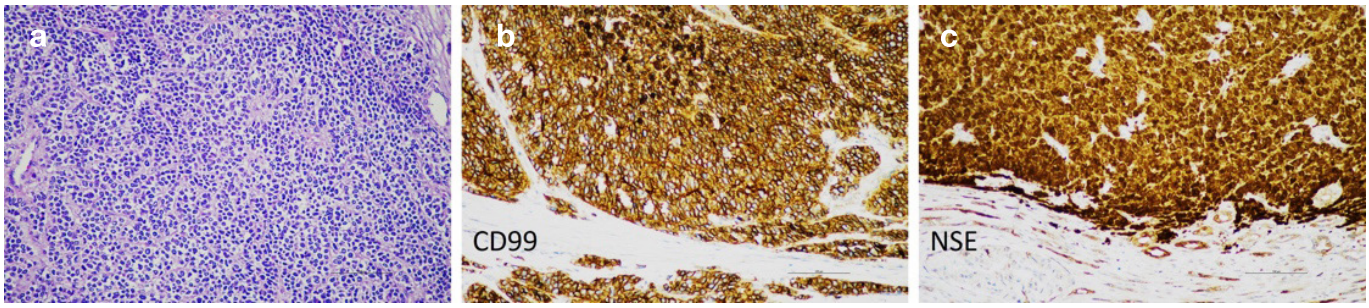

Fig. 3. Renal Ewing sarcoma is characterized by proliferation of small round blue cells with scanty cytoplasm, arranged around vascular spaces (a) which express CD99 (b) and NSE (c). Ob. 20x

extensive neuroectodermal differentiation with free resection margins was established. As metastases were identified in one of the three lymph nodes, along with lymphatic, vascular and perineural invasion, the tumor was staged as pT3N1M0L1V2R0. We did not possess any data about the cytogenetic examinations using fluorescence in situ hybridization (FISH).

Outcome and follow-up

Postoperative evolution in our case proved favorable. One month after the surgery the patient received 4 cycles of VAIA regiment: Vincristine (1,5 mg/m2) once a day 1 & 22, Doxorubicin (20 mg/m2) once per day on days 2 to 4, Ifosfamide (2000 mg/m2) once per day on days 1 to 3 and 22 to 24, and Dactinomycin (0,5 mg/m2) once per day on days 22 to 24. Two months after completing the chemotherapy sessions, the fluorodeoxyglucose (FDG)-positron emission tomography (PET) showed multiple FDG-active lumbo-aortic adenopathies and an osteolytic lesion in the right femoral head, intensely active FDG (Figure 4).

The patient subsequently underwent second line chemotherapy with Etoposide (100 mg/m2), Ifosfamide (1800 mg/m2) and Granulocyte colony-stimulating factor (G-CSF) for febrile neutropenia prophylaxis. In order to prevent pathologic fractures, 20 Gy radiotherapy was administered at the lesion site in the femoral head alongside bisphosphonate, Zoledronic acid. Also, retroperitoneal adenopathies were treated with radiotherapy for a good local control of the disease. After the completion of 5 cycles of chemotherapy an imaging assessment was performed.

Unfortunately, the disease progressed, with the increase in the size of the retroperitoneal adenopathies and the appearance of a new lesion in the left hemisacrum.

Currently, one year after the surgery, the patient is still in good condition, with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, despite the progression of the disease and the demanding chemotherapy treatment.

As of writing this article, the case is being re-examined to decide the further therapeutic course. A suitable option for this patient is to follow a third-line chemotherapy with Docetaxel and Gemcitabine combination.

Discussion

Soft tissue sarcomas (STSs) include various types of neoplasms from an anatomical and histological point of view. [12]. In terms of origin, STSs can develop from viscera (genitourinary, gynecologic and gastrointestinal) and non-visceral soft tissues (pleura, tendon, muscle, adipose, connective tissue) [12]. STSs of the genitourinary (GU) tract are rare in adults, only a small percent of the neoplasms treated by urologic surgeons, about 1% to 2%, are in fact sarcomas. [13]. According to A. Nazemi et al, GU sarcomas are most commonly found in bladder (27.4%), kidney (24.6%), paratestis (16.6%) and scrotum (10.5%). Depending on the specific histologic subtypes, STSs present a

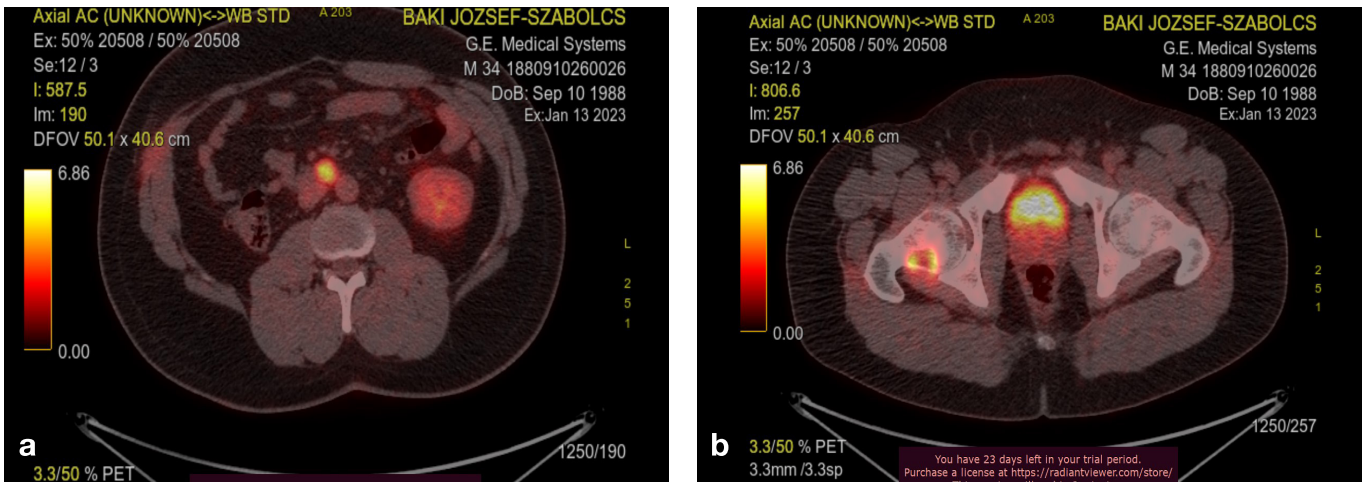

Fig. 4. Positron Emission Tomography and Computed Tomography (PET-CT) - axial section

different histologic grade. In order to predict the behavior of STSs, histologic classification must be done [12,14].

Leiomyosarcoma is the most frequent type of sarcoma found in the kidney, with a reserved prognosis. [13]. Compared to others, the EWS are always high grade, so there are linked with an increased risk for developing distant metastasis [12].

EWS with extensive neuroectodermal differentiation usually occurs in adolescents and young adults, often between 20 to 30 years, with a male: female ratio of 3:1 [3,6,9,15-18]. Renal localization of this tumor is sporadic and, as the neural markers are expressed, a neuroectodermal origin has been proposed [2,5]. As regards histogenesis, tumor cells derived from the neural tube can migrate into kidney and therefore undergo tumorigenesis. Its development from neural ramifications from celiac plexus that invest the kidney was also supposed [2,3,5,18].

The classic histologic features of this small round cell tumor include the presence of the Homer-Weight-type rosettes that surround the vascular spaces [6,9,10]. The IHC diagnosis is based, such in the present case, on synchronous positivity for CD99, NSE and GATA3, along with infrequent positivity for synaptophysin and S100 protein [2,6,9,10,17]. Further, cytogenetic studies showed that approximately 90% of EWS with extensive neuroectodermal differentiation harbor a specific translocation gene t (11;22) (q24; q12) which led to a functional EWS-FLI 1 fusion gene that can be identified by FISH and reverse transcription polymerase chain reaction (RT-PCR) [2,9,10].

Despite the technological progress in imagistic methods, the CT, MRI, and PET-CT play just a complementary role in tumor assessment [1,5,17]. On CT-scan, the large soft tissue mass is mostly multi-cystic and well defined with an ill-defined capsule. Necrosis can be found as well as calcifications, and the possible involvement of renal vein or inferior cava vein [5,6,17]. MRI shows iso- or hypointensity on T1 weighted images and heterogeneity on T2-weighted images [10,17]. Contrast-enhanced ultrasound is an inexpensive, radiation-free examination, which can differentiate the EWS from other malignancies like renal cell carcinomas [5]. PET-CT uses radiolabeled glucose analogs and can assess tumor grade by presenting tumor metabolic activity [12]. At the time of diagnosis, one-third of patients have tumor thrombi in inferior vena cava or renal vein, similar to our case [19].

The staging of EWS with extensive neuroectodermal differentiation is carried out according to the recommendations given by the American Joint Committee on Cancer (AJCC), based on the histological type, the grade of differentiation and tumor size; the most important criteria remaining the grade of differentiation. [12,14]. The preferred grading system used by AJCC is the French one, designed by Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [14]. Clinical classification is based on T, N and M characteristics (tumor size, nodular involvement, and presence/absence of distant metastases) meanwhile, the pathological classification is carried out by studying the tumor tissue removed by surgical intervention. It is necessary to consider the possibility that the chemotherapy and radiotherapy treatment can affect the tumor grade [14].

Differential diagnosis of small round cell tumors of the kidney is mainly based on IHC. Several entities like rhabdomyosarcoma, neuroblastoma, Wilm's tumor, small cell osteosarcoma, synovial sarcoma, lymphoblastic lymphoma, desmoplastic small round cell tumor should be considered [19]. However, extensive neuroectodermal differentiation of EWS was only recently documented [19].

Compared to EWS with extensive neuroectodermal differentiation, Wilms tumor cells are marked by WT1 [19,20] The diagnosis of EWS with extensive neuroectodermal differentiation should only be done after ruling out lymphoblastic lymphoma based on negativity for CD43, CD45, TdT, and PAX5 and positivity for CD99 and FLI-1. Ganglioneuroblastoma is negative for CD99 but express S100, synaptophysin, chromogranin and NSE. By comparison, the tumor cells described in this case report diffusely expressed membrane CD99 and NSE.

Rabdomyosarcoma express desmin and MyoD1, desmoplastic tumor showing vimentin, desmin, cytokeratin and infrequent and focal positivity for CD99. Neuroblastoma shows synaptophysin positivity and osteosarcoma presents nuclear SATB, but they both lack the expression of CD99 [19].

In case of an inconclusive IHC result, molecular testing is required. [19]. Because we were not given access to the FISH analysis results (to know the gene fusion EWSR1-FLI1 status) our differential diagnosis also included CIC-rearranged sarcoma, as well as other non-EWSR1 rearranged small blue round cell tumors. CIC-rearranged sarcoma, defined by CIC-related gene fusion, CIC-DUX4 being the most common, is regarded as a form of EWSR1-negative primitive round cell sarcomas; WT1, CD99 and NKX2.2 profile are informative for the testing of CIC rearrangement [21,22,23]. This tumor can show in some cases positivity for NSE. [22]. Other tumors like round cell sarcoma with EWSR1-non-ETS fusion, recently described, same as EWSR1-NFATC2, FUS-NFATC2 and EWSR1-PATZ1 fusions as well as sarcoma with BCOR genetic alterations can rise problems in the diagnosis [23].

There are no universally accepted treatment regimens for EWS with extensive neuroectodermal differentiation [5]. The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) recommend a multimodal treatment that consists in surgery, chemotherapy, and radiotherapy [5,10,17,18]. Despite aggressive treatment the prognosis remains poor [9,18].

Renal biopsy is sometimes avoided, due to the risk of hemorrhage, therefore neoadjuvant chemotherapy can't always be used. [15]. Surgery remains in some cases the gold-standard treatment but negative margins (R0) are difficult to be obtained in this anatomical region [11,12].

In our case, the patient underwent surgical intervention after the complete imaging assessment that showed the absence of distant metastasis. Although neoadjuvant chemotherapy treatment could facilitate the surgical resection and eliminate subclinical metastasis, some studies suggest that due to the difficulty of a preoperatory diagnosis, neoadjuvant treatment is not suitable in all cases [16].

The most common chemotherapeutic treatment includes agents such as vincristine (V), adriamycin (A), dactinomycin (D), cyclophosphamide (C), etoposide (E), and ifosfamide (I); the common regimens are CAV/IE or VACD/IE [5,6,10]. Antracyclines (epirubicin or doxorubicin) and ifosfamide (AI) are the first line chemotherapy regimens currently used. In post-line settings, commonly used drugs are docetaxel, gemcitabine, dacarbazine, eribulin and trabectedin [24-26].

Due to high incidence of chemotherapy-related adverse events better standardized treatment regimens are needed [10]. Tyrosine kinase inhibitors (TKI) targeting Vascular Endothelial- or Fibroblastic- Growth Factor receptors (VEGFR and FGFR), same as KIT, have been approved in refractory STS treatment. [24]. Apatinib showed efficacy in post-line treatment, the combination between lenvatinib and eribulin being studied in a phase Ib/II trial [24,27,28]. STS is considered an immune "cold" tumor and usually doesn't benefit from immunotherapy, however, there are some subgroups with CD8+T cell infiltration, intratumoral tertiary lymphoid structures, and high expression of a B cell-associated gene signature that can be treated by interfering with the microenvironment. Another option of treatment for patients with advanced disease represent individualized cellular therapy using T cell receptor-engineered T cell (TCR-T) and chimeric antigen receptor T-cell (CAR-T) [24]. There are efforts in developing novel therapeutic approaches like immunotherapy directed towards tumor cell-specific epitopes but also approaches to inhibit those chimeric proteins directly [2].

Radiotherapy is used in the presence of positive surgical margins, after surgical dissection, and in the presence of residual disease and/or loco-regional lymphadenopathy [9,11]. It is reserved as an option in salvage setting. In the retroperitoneal space the conventional dose of radiation is limited due to the radiosensitivity of the surrounding structures [11, 12].

Despite the multimodal treatment, the overall survival of patients with renal EWS with extensive neuroectodermal differentiation is dismal [3]. Factors with prognostic value are: primary tumor site and size, patient's age, stage of the disease, tumor dissemination, and the response or resistance to therapy [2,17]. When diagnosed, about 40% of patients have distant metastasis [10]. After completing the chemotherapy treatment, if no metastases are found, the 5-year survival rate can increase up to 70% [5]. For patients without metastasis the 4-year overall survival is 85%, compared with 47% for patients with metastasis or extensive disease [5].

Conclusions

As renal localization of Ewing sarcoma with extensive neuroectodermal differentiation is extremely rare, subsequent diagnosis protocols and therapies are difficult to manage. Despite the multimodal treatment strategies, the prognosis remains poor.

Authors' contribution

SAD (writing – original draft, visualization, clinical follow-up, resources and formal analysis);
STB (data curation, analysis, and literature review);
TC (investigation, validation and oncologic therapy);
VA (investigation, data curation and oncologic therapy);
CB (histopathological diagnosis);
GS (interpretation of the differential diagnosis, writing – review and editing, funding acquisition, supervision).

Conflict of interest

The authors declare no conflict of interest.

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