Ewing's sarcoma of the cervix: A case report of an unusual diagnosis in pregnancy treated with surgery, adjuvant VIDE and radiotherapy

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Abstract. Ewing's sarcoma of the cervix is a rare entity and presents with considerable challenges in diagnosis and therapy. Herein, we report a case of a cervical Ewing's sarcoma presenting with FIGO stage Ib, diagnosed during the first trimester of the patient's pregnancy. Imaging with CT scans, MRI of her abdomen and PET-CT verified the locoregional extension of the tumor. The diagnosis was confirmed by immunohistochemistry and molecular analysis. Fluorescence *in situ* hybridization and RT-PCR detected the pathognomonic EWS/FLI fusion gene. Favorable prognostic factors regarding the stage, clinocopathological and molecular characteristics of the tumor are also described. Due to the rarity of the disease, at present, there is no universal consensus on the optimal therapeutic approach. The literature has been reviewed and the therapeutic schemes and available clinical data have been discussed. The patient presented in this case report was treated aggressively with tri-modality therapy and underwent radical hysterectomy followed by adjuvant chemotherapy with Vincristine-Ifosfamide-Doxorubicin-Etoposide and radiotherapy. The patient remains free of this disease 42 months following the diagnosis of her tumor.

Introduction

Cervical sarcomas are rare and constitute <1% of all cervical malignancies (1). A specific subtype, Ewing sarcoma of the cervix, is an extremely rare tumor and for this reason

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particularly challenging regarding the choice of optimal therapeutic strategy (2).

Ewing sarcoma is a mesenchymal malignancy with specific genetic and immunohistochemical characteristics, mainly affecting the bones. However, 20-30% of Ewing sarcomas arise from an extraosseous site (3). Extraosseous Ewing sarcomas affect patients of any age. The diagnosis of Ewing sarcomas of the female genital tract is extremely rare. The identification of reciprocal translocation t(11;22) and the subsequent formation of the fusion gene EWS/FLI are pathognomonic for the diagnosis of this tumor (4).

Several different therapeutic modalities have been applied to the few reported cases in the literature (5-17). ESMO and NCCN guidelines recommend to treat these tumors like uterine sarcomas (18,19). Nevertheless, there is no universal consensus on the therapeutic approach of cervical Ewing sarcomas. The coexistence of pregnancy makes the therapeutic strategy challenging. Only 6 cases with extraosseous Ewing sarcomas during pregnancy have been reported (13,20).

Case report

A 38 year old woman referred to our hospital in the first trimester of her pregnancy (9th week) due to a tumor mass in her cervix, as an incidental finding during her scheduled first trimester abdominal ultrasound. Pelvic examination revealed that the vulva and the vagina were normal. However, the cervix was enlarged with smooth surface without necrotic lesions. Bimanual examination revealed a large cervical mass measuring 8 cm in diameter. The size of the uterus was slightly enlarged. There was no extension of the lesion into the vagina, parametria or adjacent organs. MRI of her abdomen revealed a 8x7.6 cm tumor of the cervix (Fig. 1). PET-CT verified the locoregional extension of the tumor without any indications of metastatic sites (Fig. 1). Tumor biopsy was performed during termination of her pregnancy. The patient was already the mother of 2 children and decided to end her pregnancy. Histopathologic report of tissue specimen favored the diagnosis of Ewing's sarcoma/PNET.
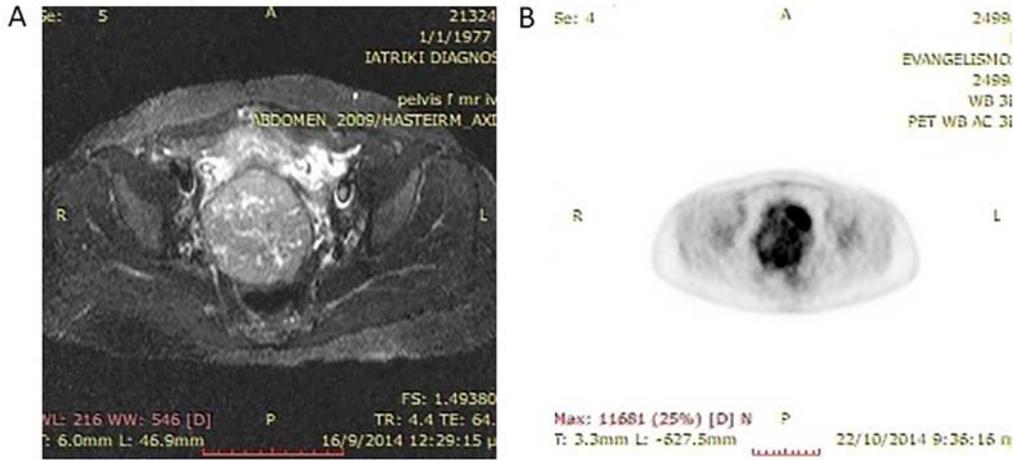
Figure 1. (A) MRI of abdomen and (B) PET-CT showing the tumor.
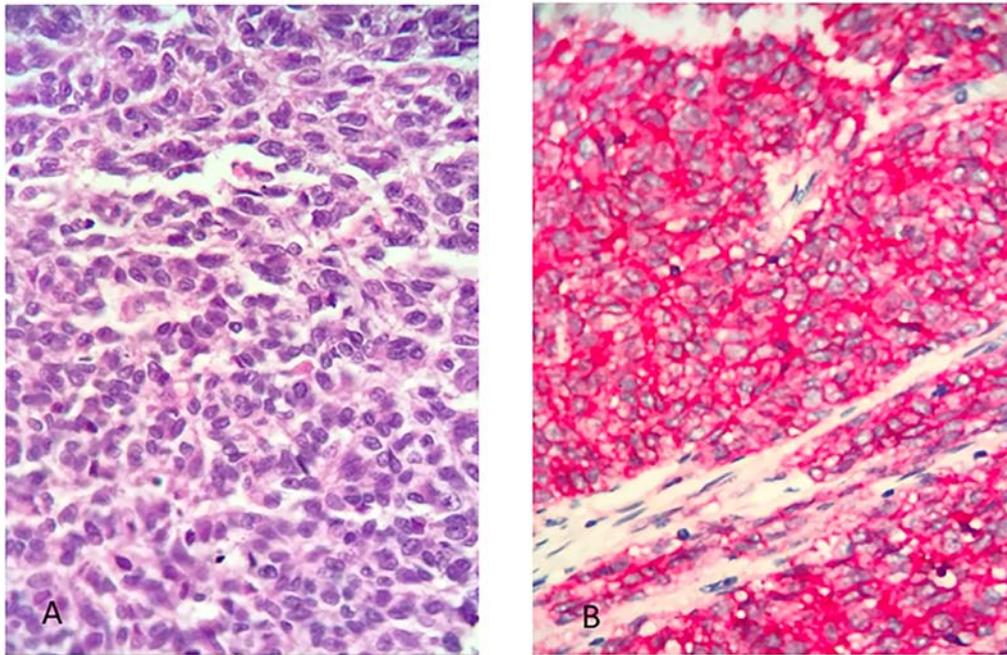
Figure 2. (A) Hematoxylin-eosin section of Ewing's sarcoma of cervix uteri, (x100 magnification). (B) Immunohistochemistry with CD99.

Clinical Staging of the disease according to FIGO stage system was IB2. Histopathology slides were reviewed by an independent pathologist who confirmed the diagnosis of Ewing's sarcoma/PNET.

The patient underwent radical hysterectomy with bilateral salpingoophorectomy and systematic pelvic lymphadenectomy. Pathology revealed a cervical tumor of 8.5x7.7x7 cm, which invaded the cervical wall with no extension beyond it. Surgical margins were free of disease. Lymph nodes were free of metastasis. The overall immunomorphologic characteristics of the tumor favor the diagnosis of Ewing's sarcoma/PNET of the cervix (Fig. 2). The Ethics Committee of Alexandra Hospital (Athens, Greece) has approved this study and the patient has signed form of consent.

To further characterize this rare case, we performed genetic analyses to the tissue specimen. Fluoresence in situ hybridization (FISH) analysis with EWS break-apart kit revealed fusion of EWS gene (Fig. 3). RT-PCR detected the formation of EWS-FLI1 chimeric gene (Fig. 3).

The patient performed post-operative CT scans of her abdomen and her chest, which showed absence of residual disease or metastases. She received 6 cycles of adjuvant chemotherapy with VIDE (21): Vincristine 1.5 mg/m^2 day 1, Ifosfamide 3 gr/m^2 day 1-3, Doxorubicin 20 mg/m^2 day 1-3, Etoposide 150 mg/m^2 day 1-3, Uromitexan day 1-3 (intravenous 20% of ifosfamide dose, per os 40% of ifosfamide dose 2 and 8 h after the infusion of ifosfamide), inj. GCSF 48MU day 7-14, and chemoprophylaxis with fluconazole 50 mgx1 day 7-14, ciprofloxacin 250 mgx2 day 7-14 and co-trimoxazole 480 mg day 1-21. During the chemotherapy patient presented with Grade I nausea, Grade III anaemia, which was treated with Erythropoiesis stimulating agent and Grade I stomatitis, which was resolved after the administration of miconazole oral gel. After the completion

Table I. Results of fluorescence *in situ* hybridization analysis.

Cases	Ex.N	Br-Ap	NORMAL	Non Sp	% ERWR1
Specimen	213	129	35	49	60.5
Control	63	13	39	11	20.6

Ex.N, total number of examined nuclei; Br-Ap, number of nuclei with Break-Apart signals; Non Sp, number of nuclei with non-specific signals.

of chemotherapy she received local pelvic radiotherapy (total dose 45 Gy). Forty two months after her diagnosis she remains free of disease.

Histopathology. Microscopic examination of the biopsy tissue specimen showed sheets of small to medium sized round primitive cells with 5 mitoses/10 HPF, harboring i) immunohistochemical positive markers: p16 and CD99 and ii) negative markers: SMA, desmin, S100, AE1/AE3, CD56, p63, LCA, CK18, chromogranin, favoring the diagnosis of Ewing's sarcoma/PNET. Histopathology slides were subsequently reviewed by an independent pathologist who described i) immunohistochemical positivity for Vimentin, Fli-1, MIC-2, EMA and NSE and ii) negativity for TdT, Desmin, CD7, CD79a, CD10, WT1, MyoD1, CD3, CD56, S-100, SMA, CEA, PR, ER, caldesmin, CK19, CK7, CK18, Chromogranin and Synaptophysin, confirming the diagnosis of Ewing's sarcoma/PNET.

Immunohistochemical staining of the tumor after total hysterectomy was positive for CD99, CD117 and vimentin, while it was negative for LCA, HMB-45, desmin, synaptophysin, chromogranin, keratin5/6 and keratin7. Surgical margins were free of disease. Lymph nodes were free of metastasis. The overall immunomorphologic characteristics of the tumor favor the diagnosis of Ewing's sarcoma/PNET of the cervix (Fig. 2).

Genetics
FISH. Formalin-fixed, paraffin-embedded biopsy blocks from the specimen were analyzed for the detection of translocations involving the *EWSR* gene at 22q12.2. A section of 4 μm was cut from the selected block and applied to silinized slides. Additional serial sections from the representative block were stained with hematoxylin-eosin in order to confirm the presence of tumor cells and to choose the appropriate area for the hybridization procedures. A section from normal tissue was used as negative control. The slides, baked at 60°C for 4 h, deparaffinized in 2 changes of fresh xylene for 10 min at RT, dehydrated for 5 min in 100% (twice), 90 and 70% ethanol solutions and allowed to air-dry before application of the pretreatment kit (Zytolight FISH-Tissue kit; Zytovision GmbH, Bremerhaven, Germany) according to the manufacturer's instructions. For hybridization procedures, the FISH probe 'ZytoLight SPEC EWSR1 Dual Color Break Apart (Zytovision GmbH) was used. Probe mixture was applied onto the areas of interest on the slides according to the manufacturer's instructions. Target areas

were, afterwards, covered with glass coverslips and sealed with rubber cement. Two post-hybridization washes were performed in 2x SSC/0.3% NP40. Slides were air-dried and counterstained using 10 μl DAPI. The prepared slides were microscopically analyzed soon afterwards. Hybridization signals were counted by the use of a Zeiss Axioplan fluorescence microscope (Carl Zeiss AG, Oberkochen, Germany) equipped with the appropriate filter combination and the ISIS digital imaging system and software (MetaSystems Hard and Software GmbH, Altlußheim, Germany). The evaluation of FISH signals meet the following criteria: i) No overlapping cells are counted, ii) a probe is considered to be split (break-a-part) when the orange and the green signals are separated by two times distance greater than the size of one hybridization signal, iii) a sample is determined to be positive for *EWSR* gene translocation if the number of nuclei that carried the break apart signals exceeds the cutoff of the control sample.

RT-qPCR. Total RNA was extracted from FFPE sections using NucleoSpin total RNA FFPE Mini Kit (Macherey-Nagel, GmbH and Co., Düren, Germany), according to the manufacturer's instructions. Approximately 500 ng of total RNA was reverse transcribed using the SuperScript II Reverse Transcriptase (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and random hexamers. cDNA was subjected to TaqMan qPCR analysis, for the detection of the EWS/Fli-1 fusion genes both type 1 and 2, using Platinum qPCR Supermix-UDG system (Invitrogen; Thermo Fisher Scientific, Inc.), with specific primers and PCR conditions as previously described (22,23).

Results

Histopathology results favor the diagnosis of Ewing's sarcoma/PNET (Fig. 2). The results of FISH of the counted nuclei are presented to the Table I. According to Table I, 20% nuclei of the control sample appeared with break-a-part signals, whilst 60% of the specimen examined nuclei, carried split signals. These results confirm the presence EWSR1 gene translocations (Fig. 3).

The type 1 EWS/FLI fusion gene was detected in the examined specimen sections, which consists of the first seven exons of EWS joined to exons 6-9 of FLI1 and accounts for approximately 60% of reported Ewing's sarcoma cases (Fig. 3).

Discussion

Extraosseus Ewing's sarcoma is an uncommon malignancy of mesenchymal origin. Cervical Ewing's sarcoma is a rare entity with very few cases reported (Table II). Diagnosis of Ewing's/PNET sarcomas in many cases is a challenge. Especially, occurrence of Ewing's sarcoma in the female genital tract makes this diagnosis even more difficult. Herein we present a case of Ewing's sarcoma of the cervix in a pregnant woman.

In our case histopathology was complemented with genetic analysis to further confirm the diagnosis of Ewing's sarcoma. FISH and Real time PCR revealed the characteristic fusion gene EWS-FLI1. The presence of this fusion is associated with
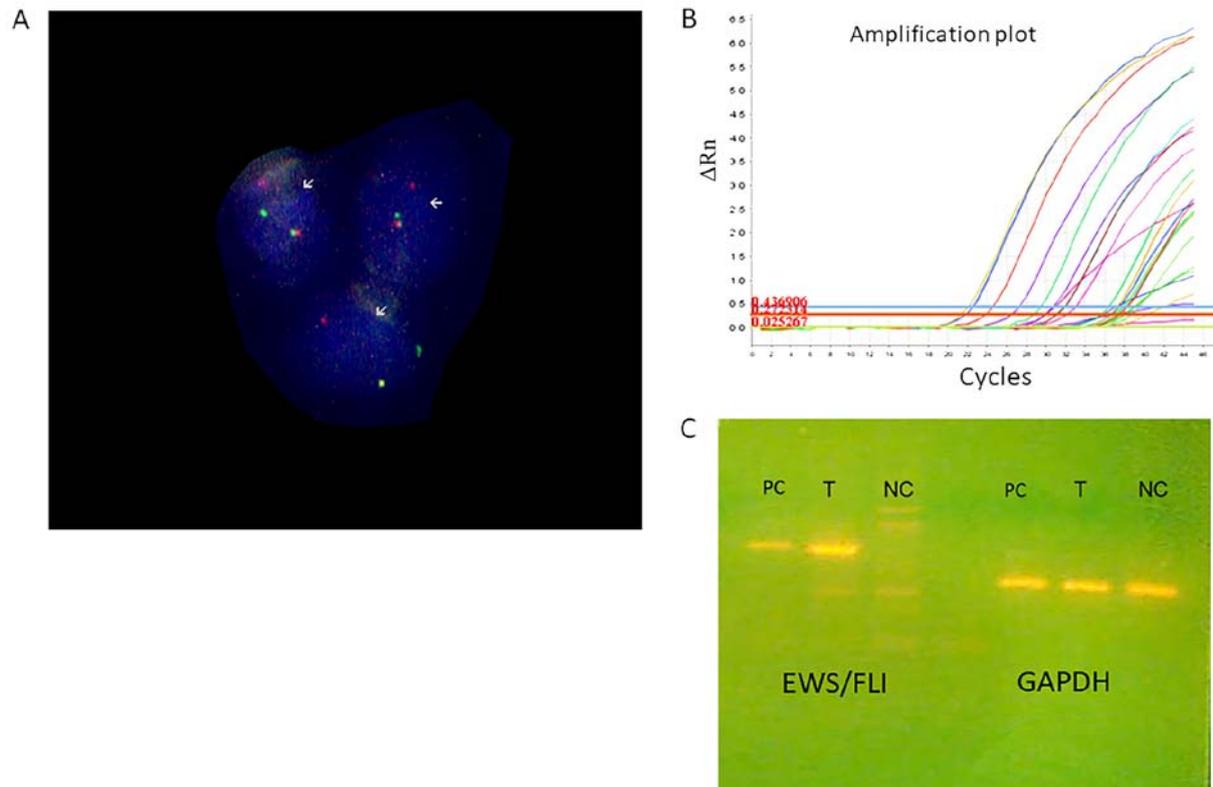
Figure 3. (A) FISH analysis with EWS break-a-part kit, Green indicated sequence mapping in 22q12.2 distal to EWSR1 gene and Red indicated sequence mapping in 22q12.1-q12.2 proximal to EWSR1 gene. Arrows illustrate cells with separation of the signal indicating fusion gene formation. The product of EWS/FLI chimeric gene of Type 1 was detected in the analyzed tissue by RT-qPCR where the (B) amplification plot and (C) gels are presented. PC, Positive control; T, Tumor sample; NC, Negative control; GAPDH gene. ΔRn, normalized reporter value; FISH, fluoresence in situ hybridization.

a better prognosis and a more favorable clinical outcome (24). However, with the use of new chemotherapeutic regimens, non-type 1 fusion type carriers seem to share similar prognosis with patients harboring EWS/FLI1 chimeric gene. In the rare occasion of Ewing sarcomas of the female genital tract there are no data regarding molecular prognostication.

The patient remains free of disease after 42 months of follow up. Ewing sarcoma is an aggressive tumor with generally poor prognosis. Our case however, harbored some favorable clinicopathological characteristics. Mitotic index of her tumor was 5 mitoses/10 HPF indicating limited proliferation status. Several studies have shown that high mitotic index is an independent prognostic factor for sarcomas (25-28). Additionally, our patient presented with Figo Stage IB2 disease. Early tumor stage is another favorable prognostic factor confirmed in several reported studies (26,27,29). Additionally, our patient was treated with radical hysterectomy and lymphadenectomy due to the large size of the tumor, in order to obtain clear margins (parametrium, upper vagina and sacro-uterine legaments) and avoid any lymph node involvement. However, it is difficult to support that lymphadenectomy has any added value to the prognosis of our patient.

Literature review revealed a few cases of cervical Ewing sarcoma which were treated with several chemotherapeutic regimens (Table II). The heterogeneity of the used regimens reflect the rarity of the disease and the evolution of multiagent chemotherapy for Ewing Sarcoma the last few decades (30-33). Our case is the only one, which was initially treated with radical hysterectomy and afterwards the patient has been treated with adjuvant VIDE, a chemotherapeutic option commonly used in extraosseus Ewing's sarcomas (21). Our patient was pregnant and her diagnosis was an incidental finding during her scheduled routine prenatal ultrasound. In the current literature, that extraosseus Ewing sarcoma diagnosis during pregnancy has been reported in 6 cases (13,20). Only 5 of these cases received chemotherapy during pregnancy. The chemotherapeutic regimens used were: Doxorubicin-ifosfamide, actinomycine D-cyclophosphamide-vincristine-bleomycin-vincristine-doxorubicin, doxorubicin-cyclophosphamide-vincristine, VIDE scheme followed by Vincristine Adriamycin Cyclophosphamide (VAC). The latter combination caused the abortion due to oligohydramnion. Since our patient decided to end her pregnancy there was no clinical dilemma regarding the selection of the chemotherapeutic regimen. The biological mechanism by which pregnancy might be connected with Ewing sarcoma or cervical neoplasia is vague. However, there are data indicating that Ewing's sarcoma precursors are highly enriched in embryonic osteochondrogenic progenitors therefore providing clues to the histogenesis of Ewing's sarcoma (34). In our case the patient presented to our Department post-operatively and neoadjuvant schemes could not be administered to her.

To conclude, we present a case of cervical Ewing sarcoma, which was diagnosed during pregnancy. Diagnostic approach included both immunohistochemistry and genetic characterization of the tumor. This is a patient that was treated aggressively with tri-modality therapy according to Ewing's sarcoma experience and she is currently free of disease 3.5 years after her diagnosis.

Table II. Reported cases of cervical Ewing sarcomas with clinical data, treatment and outcome.

Author	Age (years)	Stage	Surgery	RT	Chemotherapy	Outcome (follow up)	(Refs.)
Horn et al	26	IB1	TAH+BSO+LND	YES	Cisplatin and 5FU on metastases	Died 50 months	(14)
Cenacchi et al	36	IB2	TAH without BSO	NO	NO	Alive 18 moths	(8)
Pauwels et al	45	IB2	TAH	YES	NO	Alive 42 months	(7)
Tsao et al	24	N/A	TAH+transposition of the ovaries+LNs	YES	2 cycles of VAC alternating with IE	Alive 24 months	(9)
Malpica et al	35	IB1	TAH+BSO+LND	NO	Adjuvant Chemotherapy not reported	Alive 5 months	(10)
Malpica et al	51	IB2	TAH+BSO+LND	NO	Adjuvant Chemotherapy not reported	Alive 18 months	(10)
Snijders-Keilholz et al	21	IB2	TAH	NO	Neoadjuvant 6 cycles DIME, Adjuvant 5 Cycles VIA	Alive 27 months	(12)
Goda et al	19	N/A	NO	YES	Induction VAC for further consolidation after RT	Alive on treatment	(31)
Farzaneh et al	45	IB2	Radical Hysterectomy	NO	VAC alternating with IE Neoadjuvant and Adjuvant	Alive 4 years	(15)
Arora et al	23	N/A	TAH+BSO+LND	YES	Neoadjuvant 1 cycle of VAC followed by 2 cycles of etoposide-cisplatin	Alive 4 years	(6)
Masoura et al	23	IV	TAH+BSO	NO	Adjuvant Cisplatin 1 cycle	Died 12 days	(16)
Li et al	27	IIIB	NO	YES	Alternating VAC with IE	Alive 6 months	(11)
Khosla et al	28	IB2	TAH+BSO+LND, Termination of pregnancy	NO	Adjuvant VAC	Alive 33 months	(13)
Xiao et al	52	IIA	TAH+BSO+LND	N/A	PVB 2 cycles	Died 9 months	(32)
Xiao et al	59	IVB	TAH+BSO+LND	N/A	NO	Died	(32)
Mashriqi et al	49	IIB	TAH+BSO	YES	Adjuvant VAC alternating with IE	Died 10 months	(2)
Horn et al	57	IV	NO	YES	VIDE with VIA	Alive 18 months	(33)

5FU, 5-fluorouracil; BSO, bilateral salpingo oophorectomy; DIME, Doxorubicin; Ifosfamide Mesna Etoposide; IE, Ifosfamide Etoposide; LND, pelvic lymphadenectomy; PVB, Cisplatin Vincristine Bleomycin; RT, radiation therapy; TAH, total abdominal hysterectomy; VAC, Vincristine Adriamycin Cyclophosphamide; VIA, Vincristine Ifosfamide Dactinomycin; VP16 Etoposide; N/A, not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AK analyzed the patient, undertook analysis of the clinical, radiological and laboratory results and wrote the manuscript. GT also analyzed the patient, and analyzed the clinical, radiological and laboratory results. ML analyzed the patient, analyzed the clinical, radiological and laboratory results and drafted the manuscript. AP and LM analyzed and interpreted the molecular genetics and FISH tests and drafted the manuscript. GM and IP analyzed and interpreted the pathology tests and drafted the manuscript. NT analyzed, and operated on the patient, and contributed to the analysis of the clinical, radiological and laboratory results and drafted the manuscript Finally, AB analyzed the patient, analyzed the clinical, radiological and laboratory results and drafted the manuscript.

Ethics approval and consent to participate

The Ethics Committee of Alexandra Hospital has approved this study and the patient has signed form of consent for the analysis and publication of her data.

Patient consent for publication

The patient has provided consent for the analysis and publication of her data.

Competing interests

The authors declare that they have no competing interests.

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