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Case Report

Malignant mixed mullerian tumor: A case report about a uterine Tumor's case

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ABSTRACT

Introduction: Malignant mixed Mullerian tumor (MMMT) is an exceedingly rare and aggressive tumor which occurs predominantly in postmenopausal women though it has been reported rarely in premenopausal women.
Case presentation: A 54-year old nulliparous postmenopausal female presented with a 3-month history of vaginal bleeding, mild lower abdominal pain and weight loss. Ultrasound revealed markedly enlarged uterus with a hyper-echoic solid and cystic mass and a right adnexal complex mass. Total abdominal hysterectomy and bilateral salpingioopherectomy were done. Histopathological features were consistent with MMMT. The patient is currently stable after 6 cycles of adjuvant chemotherapy which consisted of paclitaxel and carboplatin.
Clinical discussion: MMMT of the uterus is rare, high-grade neoplasms comprising only 1–2% of uterine cancers and 3–5% of all uterine malignancies. This tumor may arise in the ovaries, fallopian tubes and vagina. Histologically, MMMT is a biphasic tumor composed of both epithelial (carcinoma) elements and mesenchymal (sarcoma) elements; though, which component is responsible for the tumor's aggressive biological behavior remains undetermined.
Conclusion: MMMT is a rare and aggressive tumor which is commonly seen in postmenopausal women with high rate of recurrence therefore, Radical surgery and close follow-up is mandatory since the role of chemo-radiotherapy remains unclear in the management of patients with this tumor. Both stage of the tumor and myometrial invasion are considered as potential prognostic factors.

1. Introduction

Malignant mixed Mullerian tumors (MMMT) which are also known as carcinosarcomas are uncommon and aggressive tumors and they account for 2–5% of tumors commonly derived from the body of the uterus [1]. MMMTs are most commonly seen in postmenopausal females with a higher incidence of these tumors among black women than white women [2]. It is a biphasic neoplasm which consists of both epithelial and mesenchymal components, the epithelial component may be endometrioid, undifferentiated, clear cell, or serous and also the tumor is divided into two types, homologous type and heterologous type [3]. In our case, the tumor was homologous type. The homologous tumor is the one whose sarcomatous component is made up of endometrial stroma and fibrous or smooth muscle tissue whereas heterologous type is one whose sarcomatous component is made up of tissue not found in the uterus such as cartilage, skeletal muscle, and/or bone [1–3]. The most common epithelial component is adenocarcinoma, but clear cell, mucinous, and papillary serous components can also occur and the most common mesenchymal component is undifferentiated sarcoma in homologous tumors and rhabdomyosarcoma in heterologous tumors [4]. Uterus and ovary are the common sites for MMMT, though it can occur anywhere along the female genital tract and in the peritoneum [5].

Herein we present the case of a 54-year female with a confirmed diagnosis of MMMT of the uterus. Additionally, we reviewed the literature specifically by highlighting on issues related to the histogenesis, diagnosis and prognosis of the tumor. This work has been reported in line with the SCARE criteria [6].

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2. Case report

A 54-year old female who was nulliparous and postmenopausal presented with a 3 month-history of vaginal bleeding, mild lower abdominal pain and weight loss. Her past medical and family history were uneventful. On physical examination, she was ill-looking, pale and slightly wasted. Full blood picture showed normal parameters except for haemoglobin which was 10 gm/dL. Liver function and renal function tests were within normal range. Pelvic ultrasound examination revealed an enlarged uterus with complex hyper-echoic mass consisting of both solid and cystic areas. The mass was extending down to lower uterine segment and the cervix. Also, the right adnexa showed a complex mass with solid and cystic areas measuring 6 × 5.5 cm which was suggestive of a complex neoplastic cystic lesion. The differential diagnoses included atypical polypoid adenomyoma and endocervical polyp.

Total abdominal hysterectomy (TAH) and bilateral salpingioopherectomy was done and haemostasis was well achieved. TAH was done by an experienced gynecologist with an assistant of a general practitioner. After thorough exploration, it was observed that there were no residual tumors. The TAH specimen was sent for histological evaluation. Grossly, the uterus was enlarged and it measured 14.0 x 10.0 × 8.0 cm, enlarged right ovary with smooth surface measuring 5.5 × 5.0 cm. The left ovary and the cervix were both normal. Cut-surface of the uterus showed irregular solid mass with unilocular cyst, and hemorrhage distorting the endometrial cavity. The cystic masses contained serous turbid colored fluids and the tumor appeared to be invading deep into the myometrium especially at the level of the fundus (Fig. 1a).

Cut-surface of the right ovary showed a mass with solid and cystic areas with irregular rough linings. The right fallopian tube was thickened and obliterated by the tumor, the left fallopian tube and ovary were unremarkable (Fig. 1b).

Microscopically, haematoxylin and eosin (H&E) stained sections showed a malignant tumor which was composed of a mixture of epithelial and sarcomatous components (Fig. 2a).

The epithelial component consisted of well-formed atypical glands lined by malignant cells with round to oval pleomorphic vesicular nuclei, prominent nucleoli, moderate amount eosinophilic cytoplasm and occasional mitotic figures (Fig. 2b).

The mesenchymal (sarcomatous) component consisted of sheets of sarcomatous spindle shaped cells. The Individual tumor cells showed elongated large and highly pleomorphic vesicular nuclei, indistinct nucleoli, irregular nuclear membrane, scant cytoplasm and multiple abnormal mitosis (Fig. 2c).

Immunohistochemistry staining showed positivity for EMA (Fig. 3a), pancytokeratin (Fig. 3b), desmin (Fig. 3c), and P53 (Fig. 3d).

There was evidence of vascular invasion, however lymph node status could not be assessed. The tumor was invading the myometrium; anteriorly and posteriorly to about two-third of its thickness. Also, cervix, right fallopian tube and the ovary were also microscopically infiltrated by the tumor. Extensive areas of necrosis and hemorrhage were also noted. The parametrial soft tissues were free of the tumor. Histopathological diagnosis of malignant mullerian mixed tumor (carcinosarcoma) was made. For staging, abdominal computed tomography (CT) scan was done which revealed no evidence of metastasis or mesenteric lymphadenopathy. TNM and International Federation of Gynecology Obstetrics (FIGO) stages which were assigned were stage T3aNxM0 and stage IIIA, respectively. The patient stayed in the ward for 3 days and she was charged home on the 4th day on amoxicillin + clavulanic acid 1 g daily for 7 days, metronidazole tabs 500 mg for 5 days, and tramadol tabs 50 mg for 2 days. On the 7th day postoperatively, she started her 6 cycles of adjuvant chemotherapy consisting of a combination of two drugs; paclitaxel and carboplatin. After completing the cycles, she was clinically evaluated three times in a period of 9 months, she remained stable without recurrence of any other symptoms related to the tumor. Either there were no episodes of drug intolerability or adverse effects that were detected in the patient. Additionally, the patient had good adherence to the medications that were given in the course of time. Currently, she is quite fine after a period of almost 18 months after treatment. Reporting of the case was done in accordance to the state the SCARE 2020 guidelines [6].

3. Discussion

Malignant uterine neoplasms containing both carcinomatous and

Fig. 1(a). Cut-surface of the uterus showing a solid mass with unilocular cyst involving mainly the posterior aspect of the uterus, the tumor involved the fundus with extensive myometrial invasion, endometrial cavity and lower uterine segment grossly (red arrows), the green short arrow is pointing to the unilocular cyst. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

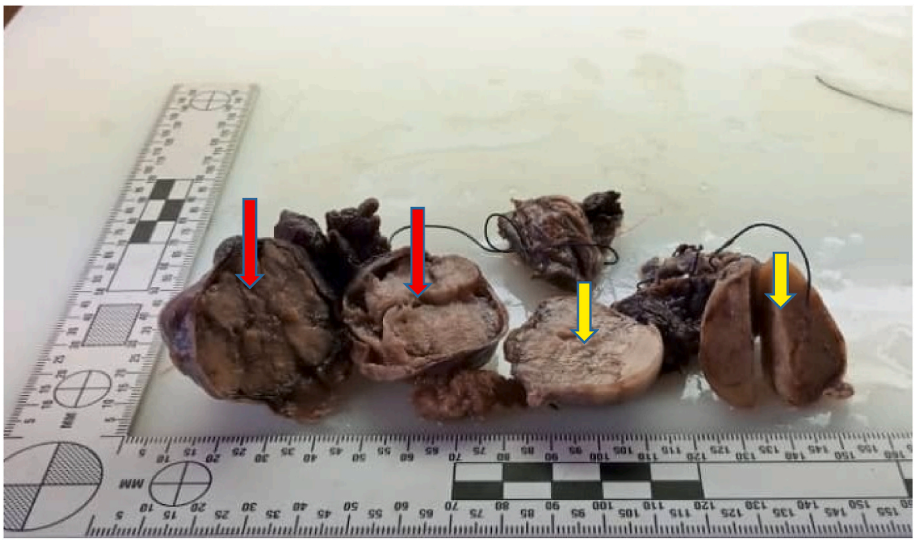

Fig. 1(b). Cut surface of both ovaries showing an enlarged right ovary with mainly solid mass and small cystic areas (red arrows), and grossly normal looking left ovary (yellow arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

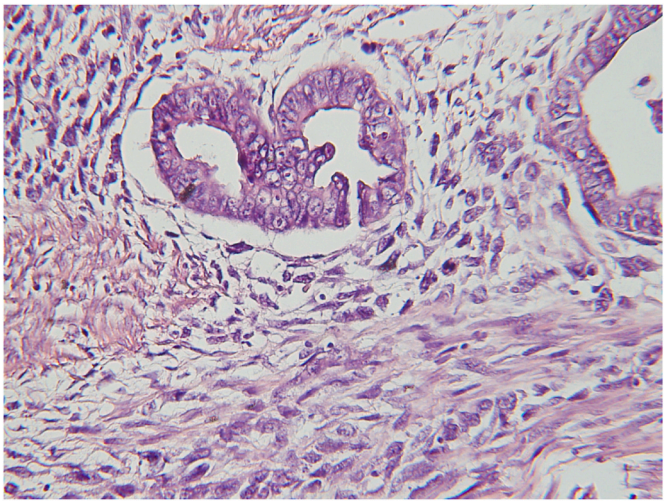

Fig. 2(a). Photomicrograph showing malignant mixed mullerian tumor consisting of epithelial component forming atypical gland, and homologous sarcomatous component composed of malignant spindle shaped cells with marked pleomorphism and occasional mitosis (**H & E stain x200**).

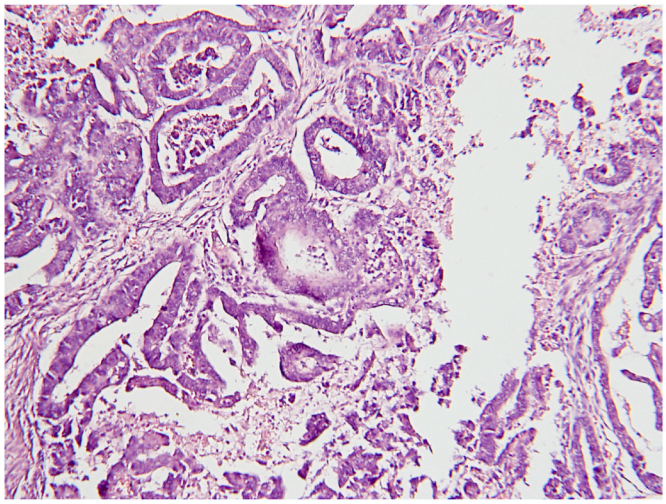

Fig. 2(b). Photomicrograph showing predominantly epithelial component of the tumor composed of well-formed atypical glands lined by malignant epithelial cells with round to oval pleomorphic vesicular nuclei, prominent nucleoli, moderate amount of eosinophilic cytoplasm and rare mitosis (**H & E stain x100**).

sarcomatous components are classified by the World Health Organization (WHO) as carcinosarcomas [7]. The first case was reported by Gerhardt in 1989, which was confirmed by Meyer with personal examination of the slides [8]. Most of the patients with MMMTs present in the fifth decade of life but it has also rarely been reported in younger age and they commonly affect the uterus, however, other parts including cervix, ovaries, fallopian tubes, vagina, peritoneum, and extra-genital sites [5]. In our case the tumor was involving both the anterior and posterior walls of the uterine corpus as well the cervix, right fallopian tube and ovary.

Predisposing factors for MMMT are said to include nulliparity, diabetes mellitus, obesity, chronic estrogen stimulation, and history of pelvic radiation although cases of tamoxifen-associated MMMT have also been reported [9]. This is based on the fact that tamoxifen can induce proliferation of endometrial glands and peri-glandular stromal condensation due to the presence of estrogen receptors in the glandular epithelium and stromal cells [2]. Tamoxifen induced endometrial carcinogenesis is supported by other studies [9]. The classical symptom triad indicative of MMMT consists of pain, severe vaginal bleeding, and passing of necrotic tissue per vaginum [1]. In this case, the patient presented with lower abdominal pain, weight loss and vaginal bleeding.

Three main theories regarding the histogenesis of MMMT have been proposed which include collision, combination, and conversion theories. The collision theory suggests that carcinoma and sarcoma are two independent neoplasms, the combination theory suggests that both components are derived from a single stem cell that undergoes divergent differentiation, and the conversion theory suggests that the sarcomatous elements are derived from the carcinoma during the evolution of the tumor [3]. McCluggage suggested that the spindle cell component is a pseudo-sarcomatous stromal reaction in the presence of carcinoma divergent differentiation [9]. Immunohistochemical and molecular analysis have speculated that MMMT may begin as adenocarcinoma and later it may acquire sarcomatoid differentiation over a period of time, exemplifying the clonal origin of these tumors [7]. Both high grade endometrial carcinoma and MMMT have a similar molecular profile,

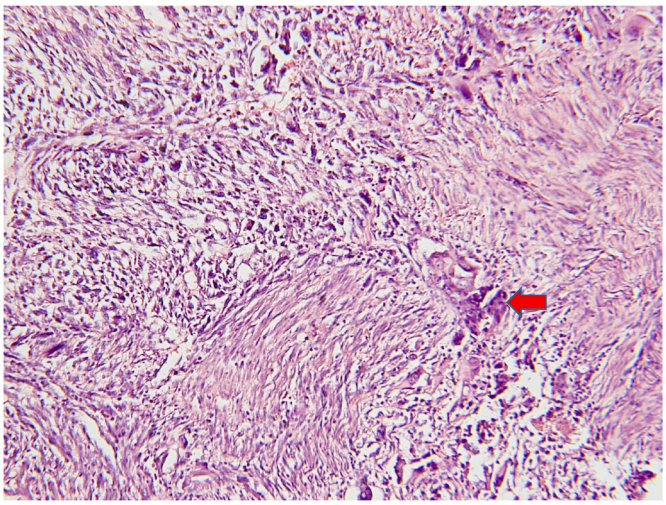

Fig. 2(c). Photomicrograph showing homologous sarcomatous component of the tumor composed of sheets of sarcomatous spindle shaped cells with elongated large and highly pleomorphic vesicular nuclei, indistinct nucleoli, irregular nuclear membrane, and scant cytoplasm and multiple abnormal mitosis, single atypical gland is also seen (arrow) (**H & E stain x100**).

with TP^{53} mutation being the most common molecular alteration [5]. However, the aggressive characteristics of MMMT compared to endometrial adenocarcinoma, and delayed time to diagnosis, reflect differences in pathogenic mechanisms [9].

Surgical management includes total abdominal hysterectomy with bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymphadenectomy [4]. Multiple chemotherapeutic regimen have been studied, with response rates ranging 12–100%, though there is no consensus on optimal adjuvant chemotherapy [2].

MMMTs express epithelial markers such as epithelial membrane antigen and pancytokeratin as well as stromal lineage markers such as desmin and S-100 [1]. In our case, EMA and pancytokeratin were positive only in the adenocarcinoma component while the sarcomatous component was negative. Desmin was positive only in the sarcomatous component and negative in the adenocarcinoma component. P53 was diffusely positive in both components. P53 expression detected immunohistochemically doesn't necessarily correlate with presence of TP53 mutation, however, the strong and diffuse pattern of P53 positivity might be an indicator for presence of TP53 mutation commonly observed in this tumor and endometrial adenocarcinoma [9].

MMMT has a poor prognosis and most of the patients have extrauterine spread at the time of diagnosis [9]. Extension to pelvis, lymphatic and vascular permeation, distant lymph node, and

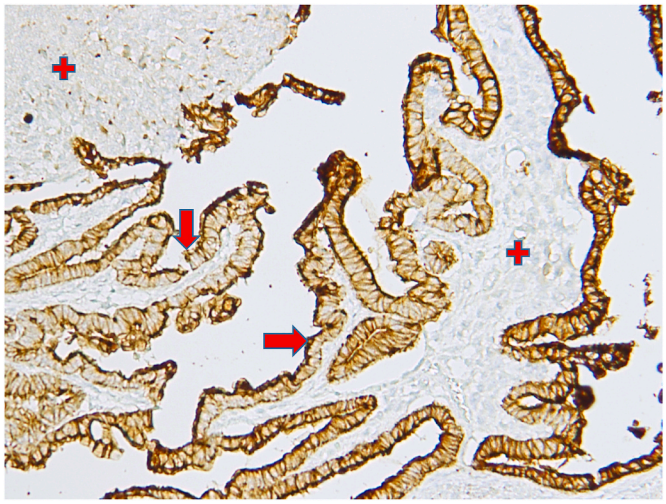

Fig. 3(b). Photomicrograph showing strong membranous pancytokeratin immunostaining in adenocarcinoma component (arrows) and negative sarcomatous component (red crosses) (**Immunohistochemistry staining for pancytokeratin, x100**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

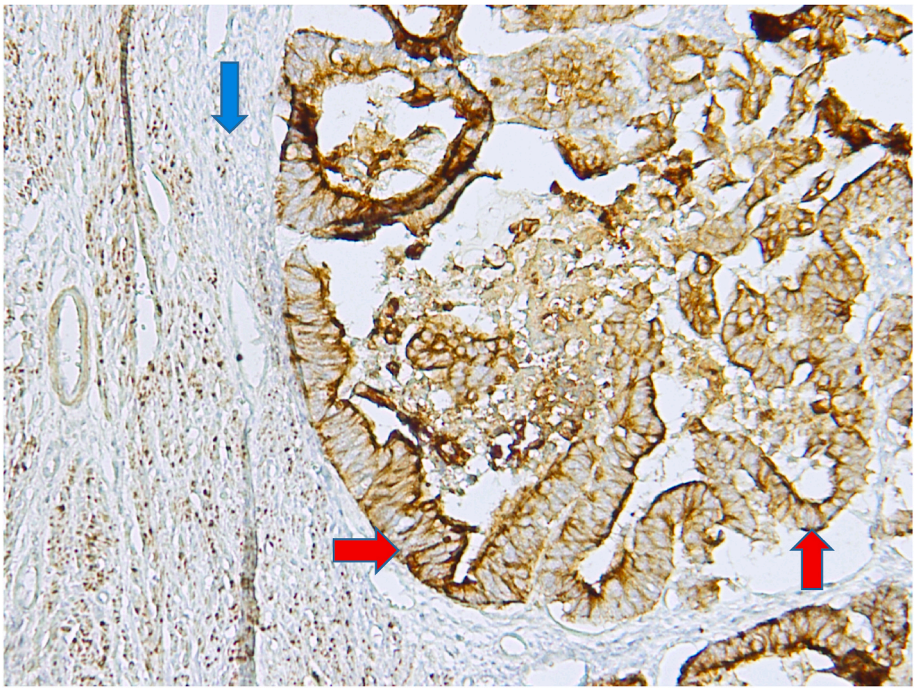

Fig. 3(a). Photomicrograph showing strong membranous immunostaining of epithelial membrane antigen (EMA) in adenocarcinoma component (red arrows) with negative sarcomatous component (blue arrow) (**Immunohistochemistry staining for EMA, x40**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

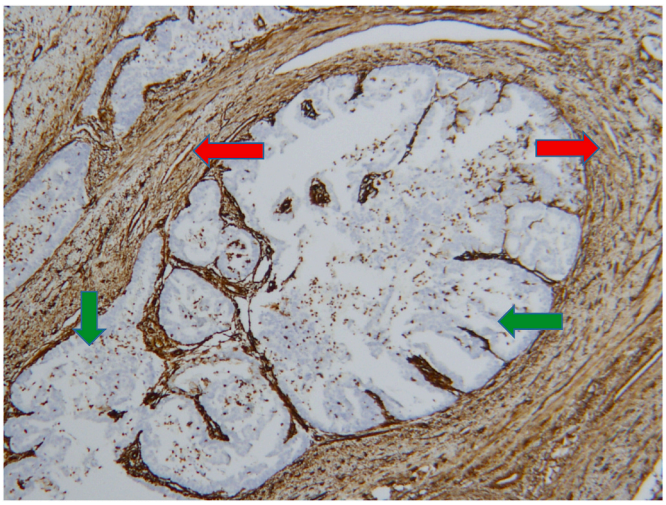

Fig. 3(c). Photomicrograph showing desmin strong nuclear immunostaining in sarcomatous component red arrows, and negative adenocarcinoma component green arrows (**Immunohistochemistry staining for desmin, x100**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

blood-borne metastasis are common [1]. In our case, there was extension into the cervix, fallopian tube, ovary as well as vascular invasion, lymph node involvement could not be assessed, and there was no distant metastasis. Metastatic spread of MMMT is similar to high-grade endometrial carcinoma and most patients die due to local pelvic or abdominal recurrence. The risk of higher stage disease and metastasis is closely related to depth of myometrial invasion [8]. In the study by Ferguson et al. cases of stage I uterine MMMT were more aggressive compared to stage I grade III endometrioid, serous or clear cell carcinoma [10]. Moreover, the 3-year disease free survival was 42% for cases with MMMT compared to 87% for cases with high-grade adenocarcinoma [11]. The average 5-year overall survival for patients with MMMTs was previously to be 21% and 70%–90% of tumor related deaths occurred within 18 months of diagnosis [12]. Determining the extent of invasion by the tumor serves as the key prognostic factor when considering the clinical outcome of the patients diagnosed with MMMT.

The strengths of this case report is that we included comprehensive approach in confirming the diagnosis by involving a wide range of immunohistochemistry antibodies and also the follow-up period of 15 months helps in providing quite enough time to conclude regarding development of either recurrence or metastasis. However, inability to include CT scan for surveying of possible recurrence or metastasis may be considered a weakness in our approach to the present case report.

4. Conclusion

Management of this type of tumor is challenging, as this is a rare disease and its treatment is hardly described in standard gynecological textbooks. As a result, clear management guidelines as well as survival rate after treatment often not available. Furthermore, the role of adjuvant radiation and chemotherapy is still unclear. Other institutes have used radiotherapy for treatment of recurrence. Although this patient is currently stable and responded well to treatment offered (total abdominal hysterectomy and bilateral salpingooophorectomy and adjuvant chemotherapy), she is scheduled for a close follow-up for at least 18 months as high rate of recurrence has been reported in patients with MMMT.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Ethical approval was exempted by the ethical research board.

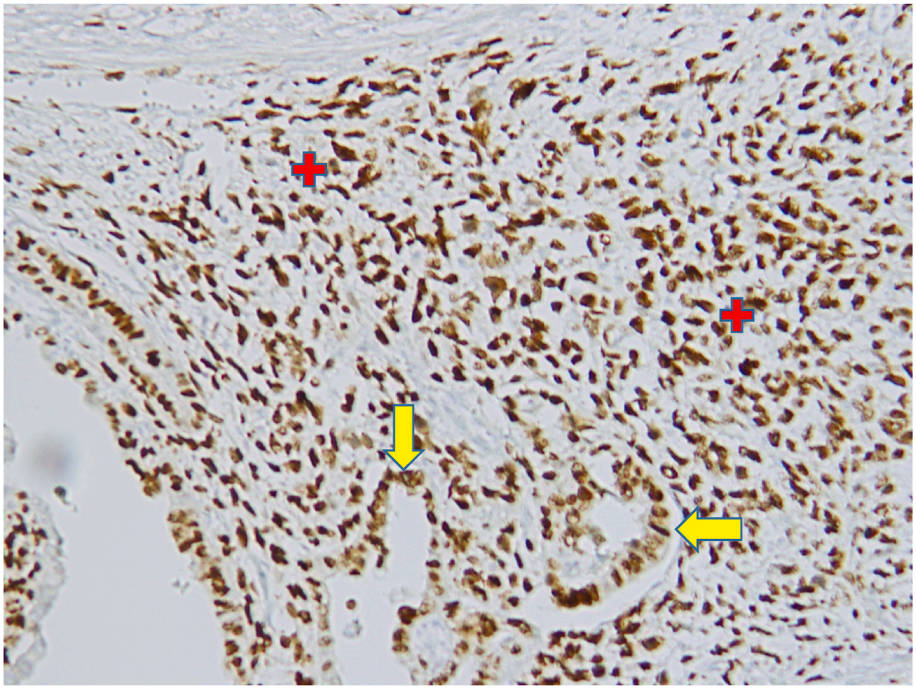

Fig. 3(d). Photomicrograph showing strong and diffuse P53 nuclear immunostaining in both adenocarcinoma component (arrows) and sarcomatous component (red crosses) (**Immunohistochemistry staining for P53, x100**). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Author contribution

EDM: made the initial histological diagnosis, reviewed the literature, and wrote the initial manuscript, **TO**: participated in the initial histological diagnosis, took photomicrographs, reviewed the literature, and all the versions of the manuscript. **JJY**: organized the manuscript, wrote the first draft of the manuscript, and made substantial review of the literature, and **EO**: confirmed the histological diagnosis, and made critical review of the manuscript. All authors reviewed critically the final version of the manuscript and they agree the intellectual content of the information contained in the paper.

Registration of research studies

Not applicable.

Guarantor

James J Yahaya agrees to be the guarantor of the work being submitted.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

All authors have no conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2022.100493.

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