

World Journal of *Clinical Cases*

World J Clin Cases 2020 October 6; 8(19): 4280-4687



OPINION REVIEW

- 4280 Role of monoclonal antibody drugs in the treatment of COVID-19
Ucciferri C, Vecchiet J, Falasca K

MINIREVIEWS

- 4286 Review of simulation model for education of point-of-care ultrasound using easy-to-make tools
Shin KC, Ha YR, Lee SJ, Ahn JH
- 4303 Liver injury in COVID-19: A minireview
Zhao JN, Fan Y, Wu SD

ORIGINAL ARTICLE

Case Control Study

- 4311 Transanal minimally invasive surgery *vs* endoscopic mucosal resection for rectal benign tumors and rectal carcinoids: A retrospective analysis
Shen JM, Zhao JY, Ye T, Gong LF, Wang HP, Chen WJ, Cai YK
- 4320 Impact of *mTOR* gene polymorphisms and gene-tea interaction on susceptibility to tuberculosis
Wang M, Ma SJ, Wu XY, Zhang X, Abesig J, Xiao ZH, Huang X, Yan HP, Wang J, Chen MS, Tan HZ

Retrospective Cohort Study

- 4331 Establishment and validation of a nomogram to predict the risk of ovarian metastasis in gastric cancer: Based on a large cohort
Li SQ, Zhang KC, Li JY, Liang WQ, Gao YH, Qiao Z, Xi HQ, Chen L

Retrospective Study

- 4342 Predictive factors for early clinical response in community-onset *Escherichia coli* urinary tract infection and effects of initial antibiotic treatment on early clinical response
Kim YJ, Lee JM, Lee JH
- 4349 Managing acute appendicitis during the COVID-19 pandemic in Jiaying, China
Zhou Y, Cen LS
- 4360 Clinical application of combined detection of SARS-CoV-2-specific antibody and nucleic acid
Meng QB, Peng JJ, Wei X, Yang JY, Li PC, Qu ZW, Xiong YF, Wu GJ, Hu ZM, Yu JC, Su W
- 4370 Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients
Wang L, He WB, Yu XM, Hu DL, Jiang H

- 4380** Percutaneous radiofrequency ablation is superior to hepatic resection in patients with small hepatocellular carcinoma

Zhang YH, Su B, Sun P, Li RM, Peng XC, Cai J

- 4388** Clinical study on the surgical treatment of atypical Lisfranc joint complex injury

Li X, Jia LS, Li A, Xie X, Cui J, Li GL

- 4400** Application of medial column classification in treatment of intra-articular calcaneal fractures

Zheng G, Xia F, Yang S, Cui J

Clinical Trials Study

- 4410** Optimal hang time of enteral formula at standard room temperature and high temperature

Lakananurak N, Nalinthassanai N, Suansawang W, Panarat P

META-ANALYSIS

- 4416** Meta-analysis reveals an association between acute pancreatitis and the risk of pancreatic cancer

Liu J, Wang Y, Yu Y

SCIENTOMETRICS

- 4431** Global analysis of daily new COVID-19 cases reveals many static-phase countries including the United States potentially with unstoppable epidemic

Long C, Fu XM, Fu ZF

CASE REPORT

- 4443** Left atrial appendage aneurysm: A case report

Belov DV, Moskalev VI, Garbuzenko DV, Arefyev NO

- 4450** Twenty-year survival after iterative surgery for metastatic renal cell carcinoma: A case report and review of literature

De Raffele E, Mirarchi M, Casadei R, Ricci C, Brunocilla E, Minni F

- 4466** Primary rhabdomyosarcoma: An extremely rare and aggressive variant of male breast cancer

Satală CB, Jung I, Bara TJ, Simu P, Simu I, Vlad M, Szodorai R, Gurzu S

- 4475** Bladder stones in a closed diverticulum caused by *Schistosoma mansoni*: A case report

Alkhamees MA

- 4481** Cutaneous ciliated cyst on the anterior neck in young women: A case report

Kim YH, Lee J

- 4488** Extremely rare case of successful treatment of metastatic ovarian undifferentiated carcinoma with high-dose combination cytotoxic chemotherapy: A case report

Kim HB, Lee HJ, Hong R, Park SG

- 4494** Acute amnesia during pregnancy due to bilateral fornix infarction: A case report
Cho MJ, Shin DI, Han MK, Yum KS
- 4499** Ascaris-mimicking common bile duct stone: A case report
Choi SY, Jo HE, Lee YN, Lee JE, Lee MH, Lim S, Yi BH
- 4505** Eight-year follow-up of locally advanced lymphoepithelioma-like carcinoma at upper urinary tract: A case report
Yang CH, Weng WC, Lin YS, Huang LH, Lu CH, Hsu CY, Ou YC, Tung MC
- 4512** Spontaneous resolution of idiopathic intestinal obstruction after pneumonia: A case report
Zhang BQ, Dai XY, Ye QY, Chang L, Wang ZW, Li XQ, Li YN
- 4521** Successful pregnancy after protective hemodialysis for chronic kidney disease: A case report
Wang ML, He YD, Yang HX, Chen Q
- 4527** Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report
Li B, Li GW, Xue L, Chen YY
- 4535** Percutaneous fixation of neonatal humeral physeal fracture: A case report and review of the literature
Tan W, Wang FH, Yao JH, Wu WP, Li YB, Ji YL, Qian YP
- 4544** Severe fundus lesions induced by ocular jellyfish stings: A case report
Zheng XY, Cheng DJ, Lian LH, Zhang RT, Yu XY
- 4550** Application of ozonated water for treatment of gastro-thoracic fistula after comprehensive esophageal squamous cell carcinoma therapy: A case report
Wu DD, Hao KN, Chen XJ, Li XM, He XF
- 4558** Germinomas of the basal ganglia and thalamus: Four case reports
Huang ZC, Dong Q, Song EP, Chen ZJ, Zhang JH, Hou B, Lu ZQ, Qin F
- 4565** Gastrointestinal bleeding caused by jejunal angiosarcoma: A case report
Hui YY, Zhu LP, Yang B, Zhang ZY, Zhang YJ, Chen X, Wang BM
- 4572** High expression of squamous cell carcinoma antigen in poorly differentiated adenocarcinoma of the stomach: A case report
Wang L, Huang L, Xi L, Zhang SC, Zhang JX
- 4579** Therapy-related acute promyelocytic leukemia with FMS-like tyrosine kinase 3-internal tandem duplication mutation in solitary bone plasmacytoma: A case report
Hong LL, Sheng XF, Zhuang HF
- 4588** Metastasis of esophageal squamous cell carcinoma to the thyroid gland with widespread nodal involvement: A case report
Zhang X, Gu X, Li JG, Hu XJ

- 4595** Severe hyperlipemia-induced pseudoerythrocytosis - Implication for misdiagnosis and blood transfusion: A case report and literature review
Zhao XC, Ju B, Wei N, Ding J, Meng FJ, Zhao HG
- 4603** Novel brachytherapy drainage tube loaded with double 125I strands for hilar cholangiocarcinoma: A case report
Lei QY, Jiao DC, Han XW
- 4609** Resorption of upwardly displaced lumbar disk herniation after nonsurgical treatment: A case report
Wang Y, Liao SC, Dai GG, Jiang L
- 4615** Primary hepatic myelolipoma: A case report and review of the literature
Li KY, Wei AL, Li A
- 4624** Endoscopic palliative resection of a giant 26-cm esophageal tumor: A case report
Li Y, Guo LJ, Ma YC, Ye LS, Hu B
- 4633** Solitary hepatic lymphangioma mimicking liver malignancy: A case report and literature review
Long X, Zhang L, Cheng Q, Chen Q, Chen XP
- 4644** Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report
Cai X, Yu JJ, Tian H, Shan ZF, Liu XY, Jia J
- 4652** Intravesically instilled gemcitabine-induced lung injury in a patient with invasive urothelial carcinoma: A case report
Zhou XM, Wu C, Gu X
- 4660** Bochdalek hernia masquerading as severe acute pancreatitis during the third trimester of pregnancy: A case report
Zou YZ, Yang JP, Zhou XJ, Li K, Li XM, Song CH
- 4667** Localized primary gastric amyloidosis: Three case reports
Liu XM, Di LJ, Zhu JX, Wu XL, Li HP, Wu HC, Tuo BG
- 4676** Displacement of peritoneal end of a shunt tube to pleural cavity: A case report
Liu J, Guo M
- 4681** Parathyroid adenoma combined with a rib tumor as the primary disease: A case report
Han L, Zhu XF

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Primary rhabdomyosarcoma: An extremely rare and aggressive variant of male breast cancer

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Abstract

BACKGROUND

Rhabdomyosarcoma (RMS) of the breast, a mesenchymal neoplasm with skeletal muscle differentiation, is an extremely rare tumour in males, with less than 30 cases published in English-language literature. We report on the first case of a male breast RMS, with an unusual ectomesenchymal/neuroectodermal component.

CASE SUMMARY

A 55-year-old, previously healthy male, underwent a radical left mastectomy for an ulcerated tumour mass, occupying the breast and left anterior thoracic wall. The biopsy specimen indicated the presence of a tumour with neural origins,

None declared.

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namely a peripheral neuroectodermal tumour (PNET). The surgical specimens identified two components. The rhabdomyosarcomatous component (over 70%) was represented by large pleomorphic cells with positivity for desmin, sarcomeric actin and myogenin. The PNET-like ectomesenchymal component, which was admixed with the RMS cells, and was also revealed during the preoperative biopsy, consisted of small cells which expressed neurofilament, neuron specific enolase and CD99. The microscopic examination, along with the immunohistochemical profile, allowed the diagnosis of an RMS, with unusual ectomesenchymal differentiation. The patient refused the postoperative oncologic therapy and died three months after surgery.

CONCLUSION

In patients with RMS of the breast, the PNET-like ectomesenchymal component increases the diagnosis difficulty, especially in biopsy specimens. This differentiation can be immunohistochemically proven and might highlight the possible development of high-grade sarcoma of the breast from remnants of the embryological ectodermal layer.

Key Words: Mammary gland; Rhabdomyosarcoma; Ectomesenchymoma; Male; Case report; CD99

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Core Tip: In this paper we presented an exceedingly rare and aggressive case of mammary rhabdomyosarcoma (RMS) in a male patient. We found no cases previously published in international journals, reporting an RMS with a peripheral neuroectodermal tumour-like ectomesenchymal component, namely neuroectodermal differentiation. The specific nature of the case was indicated by the presence of the ectomesenchymal component in the biopsy specimen, the case being firstly diagnosed as a tumour with neural differentiation. These findings emphasize the need for an attentive microscopic evaluation of mesenchymal tumours in the mammary region, to further confirm or infirm the presence of a second highly-malignant tumour population.

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INTRODUCTION

Rhabdomyosarcoma (RMS) is a rare soft tissue tumour which represents less than 1% of all mesenchymal tumours. It mostly occurs in children and young adults between the ages of 15 and 24 years^[1-3]. The most common histological variant, the alveolar subtype is found in children and the pleomorphic subtype predominates in older adults^[3,4].

The majority of RMS cases affect the soft tissue of the head and neck (35%-40% of cases), followed by the genitourinary system (25%), trunk and extremities (with 20%)^[5]. RMSs which occur in the mammary region are exceedingly rare, with less than 30 cases reported up to February 2020^[2].

Independently by localization, the presence of a second phenotype within the RMS, with both rhabdomyoblasts and cells with ectodermic differentiation, defines malignant ectomesenchymoma (MEM)^[6]. The origin of the second population is thought to be the migratory neural crest cells, embryologically derived from ectoderm, the outer layer of the embryo^[5,6]. Limited data have been published regarding this dual tumour, with fewer than 20 cases having ever been reported in English-language journals^[5], however, none of these were located in the mammary region.

In this paper, we present the case of a male patient, diagnosed with mammary gland RMS with ectomesenchymal differentiation, and we emphasize the complex immune profile needed for a positive and differential diagnosis. The signed, informed

consent of the patient was obtained before surgery, for both surgical intervention and the publication of data.

CASE PRESENTATION

Chief complaints

A 55-year-old male presented with a painful, ulcerated tumour mass, located on the anterior thoracic wall in the left mammary region (Figure 1).

History of present illness

The patient reported a six month history of pain in the left mammary region, caused by a progressively growing, ulcerated tumour mass, with no other significant symptoms. Three months before presentation in our department, he underwent a biopsy and suspicion of a tumour of neural origin, namely a peripheral neuroectodermal tumour (PNET) was raised, based on the positivity of tumour cells for Neurofilament and neuron specific enolase (NSE) and negativity for Cytokeratin AE1/AE3.

History of past illness

He was an ex-smoker of seven years and a social drinker, with arterial hypertension and ischaemic heart disease, which were controlled by medication.

Personal and family history

No previous illnesses were declared and there was no family history of oncologic diseases.

Physical examination

The physical examination revealed an ulcerated tumour mass, with infiltrative aspect, occupying the left mammary region (Figure 1). No other signs or symptoms were observed.

Laboratory examinations

A mild elevation of serum level of alanine-aminotransferase (55.4 U/L; normal ranges 0-41 U/L), aspartate-aminotransferase (70.0 U/L; normal ranges 0-40 U/L) and gamma-glutamyl-transpeptidase (130 U/L; normal ranges 0-71 U/L) was observed, without any other serological modifications.

Imaging examinations

The preoperative CT-scan revealed a 67 mm × 74 mm × 80 mm nodular mass, located on the anterior thoracic wall, laterally from the sternum, with high density (40 UH) and multiple disseminated micro-calcifications. Direct spread in the soft tissues and tumour-induced costal erosions were also documented, along with axillary and subclavicular adenopathies. The third intercostal space was infiltrated, with no involvement of parietal or visceral pleura.

After surgery, the CT-scan showed a 28 mm × 135 mm (antero-posterior/Lateral-lateral) haematoma affecting the axillary region and intercostal muscles. No mediastinum involvement or suspicion of bone or lung metastases were highlighted.

Gross and histopathological assessment of surgical specimens

Grossing of the left mastectomy specimen showed a 67 mm × 74 mm × 80 mm tumour mass, located on the inner medial quadrant of the mammary gland, which was associated with a 33 mm × 30 mm ulceration of the skin (Figure 1). On section, it was observed as a poorly circumscribed, yellow-grey tumour mass, with small haemorrhagic areas, which infiltrated the deep soft tissues. The attached muscular components were also macroscopically involved, as were the rib fragments.

Under the microscope, the predominant component, which represented over 70% of the tumour mass, consisted of clusters of large, intensely pleomorphic (> 20 mitoses/high power field), elongated cells, with perivascular proliferation but not tumour emboli. Multinucleated cells were also visible. These large cells were admixed with small cells, with amphophilic and scanty cytoplasm and round to oval, centrally located nuclei. This component proved the formation of Homer-Wright-like rosettes, which were composed of specific circular strands of tumour cells with round-oval nuclei, surrounding fibrillary cores. The tumour exhibited an infiltrative growth

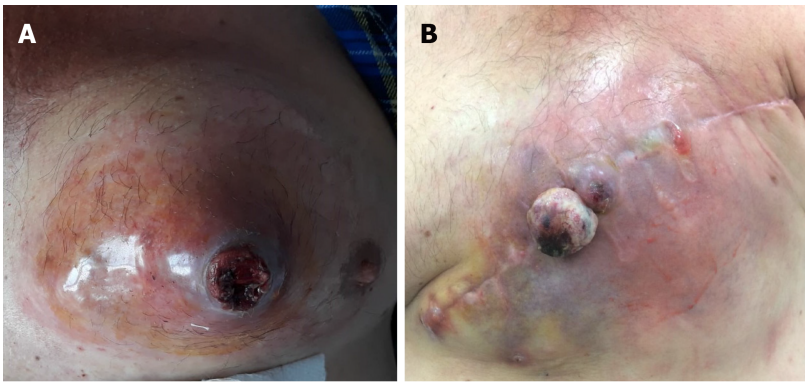


Figure 1 Macroscopic features. A: Ulcerated rhabdomyosarcoma of the male breast; B: Tumor relapse, one month after mastectomy.

pattern, with involvement of the subcutaneous tissue and the deep resection margins (Figure 2).

Immunohistochemical profile of tumour cells

Both tumour populations expressed vimentin and did not display positivity for the epithelial markers, such Cytokeratin AE1/AE3 and Cytokeratin 7 (Tables 1 and 2). In the predominant component, namely the large and pleomorphic cells, with a Ki67 proliferation index of over 90%, the rhabdoid differentiation was proved in terms of positivity for desmin, sarcomeric actin and myogenin (Figure 3). The tumour cells were not marked by the neural- (neurofilament, NSE), neuroendocrine- (synaptophysin, chromogranin), mesothelial- (calretinin) or vascular markers (CD31, CD34) and did not show a melanoma immunoprofile (negative for S100 and HMB45) (Table 2).

The second component, composed of small cells, showed a Ki67 index of around 40% and a PNET-like aspect. The immunoprofile was similar to those of cells identified in the biopsy specimens. In contrast with the predominant component, these cells showed focal positivity for neurofilament, NSE and CD99 (Figure 4), without rhabdoid differentiation. They did not express desmin, Smooth Muscle Actin (SMA), sarcomeric actin or myogenin (Table 2).

FINAL DIAGNOSIS

Based on the histological examination and immunohistochemical profile, the final diagnosis was high-grade mammary gland pleomorphic RMS with neuroectodermal/ectomesenchymal differentiation and deep positive resection margins.

TREATMENT

Based on the imagistic investigations, a radical mastectomy of the left breast was decided upon. The patient signed the informed consent prior to surgery. Following the correct preoperative preparation, an elliptical incision was made, centred around the ulcerated tumour mass. As the soft tissues were deeply infiltrated, the detachment of the tumour block was carried out simultaneously with fragments of the directly infiltrated pectoral and intercostal muscles and partial resection of the tumour-invaded anterior costal arches of ribs III-IV. Then, an excision of the axillary lymph nodes was conducted and the surgical specimens were transported to the Department of Pathology for further examination.

OUTCOME AND FOLLOW-UP

One month after surgery, the patient presented in our centre, with local recurrence (Figure 1). As the lung and bone metastases were developed and following explanation of the further therapeutic regimen possibilities, he refused both

Table 1 Immunohistochemical markers used to confirm the rhabdomyosarcoma with neuroectodermal differentiation

| Antibody | Clone | Dilution | Manufacturer | Retrieval | RMS comp | NED comp | Line of differentiation confirmed |
|----------|---------------|----------|------------------------|-----------|----------|----------|-----------------------------------|
| VIM | V9 | RTU | DAKO/ Denmark | High pH | + | + | Mesenchymal origin |
| DESM | D33 | RTU | DAKO | High pH | + | - | Myogenic origin |
| MYO | F5D | 1:100 | ImmunoLogic/Netherland | High pH | + | - | Rhabdomyosarcoma component |
| SA | Alpha Sr-1 | 1:100 | DAKO | Citrate | + | - | Rhabdomyosarcoma component |
| NF | 2F11 | 1:100 | DAKO | Citrate | - | + | Neuroectodermal component |
| NSE | BBS/NC/V1-414 | RTU | DAKO | High pH | - | + | Neuroectodermal component |
| CD99 | 12E7 | RTU | DAKO | High pH | - | + | Neuroectodermal component |

Comp: Component; DESM: Desmin; MYO: Myogenin; NED: Neuroectodermal; NF: Neurofilament; NSE: Neuron specific enolase; SA: Sarcomeric actin; RMS: Rhabdomyosarcoma; RTU: Ready to use; VIM: Vimentin.

Table 2 Immunohistochemical markers used for differential diagnosis of rhabdomyosarcoma with neuroectodermal differentiation, based on their negativity in the two components

| Antibody | Clone | Dilution | Manufacturer | Retrieval | Line of differentiation ruled out |
|--------------|--------------|----------|-------------------------|-----------|-----------------------------------|
| Pan-CK | AE1/AE3 | RTU | ImmunoLogic/ Netherland | High pH | Epithelial origin/carcinoma |
| EMA | E29 | RTU | ImmunoLogic | High pH | |
| CK7 | OV-TL | RTU | A. Menarini/ Italy | High pH | |
| p63 | 4A4 | RTU | ImmunoLogic | High pH | Squamous cell differentiation |
| SMA | 1A4 | RTU | Cell Marque/ Netherland | High pH | Leyomyosarcoma |
| CALd | 4-CD | 1:100 | DAKO/ Denmark | Citrate | |
| CALr | DAK Calret-1 | 1:100 | DAKO | High pH | Mesothelial origin |
| ER | 1D5 | RTU | Thermo Scientific/UK | High pH | Breast carcinoma |
| PR | PGR 312 | RTU | Leica/UK | High pH | |
| S100 protein | polyclonal | 1:6000 | DAKO | Citrate | Melanoma |
| HMB45 | HMB45 | RTU | Cell Marque | Citrate | |
| CD45/ LCA | UCHL-1 | RTU | Immunologic | High pH | Lymphoma |
| CD3 | F7.2.38 | RTU | DAKO | High pH | |
| CD20 | L26 | RTU | Cell Marque | High pH | |
| CD31 | JC70 | RTU | A. Menarini | Citrate | Vascular origin |
| CD34 | QBEnd10 | RTU | DAKO | High pH | |
| CD68 | KP1 | RTU | Immunologic | Citrate | Histiocytic origin |
| SYN | DAK-Synap | RTU | DAKO | High pH | Neuroendocrine differentiation |

CALd: Caldesmon; CALr: Calretinin; CK: Cytokeratin; EMA: Epithelial membrane antigen; ER: Estrogen receptor; HMB45: Human melanoma black 45; LCA: Leukocyte common antigen; PR: Progesteron receptor; RTU: Ready to use; SMA: Smooth muscle actin; SYN: Synaptophysin.

postoperative oncologic treatment and tumour re-excision with surgical reconstruction.

Without any oncological treatment, the patient died three months after the mastectomy.

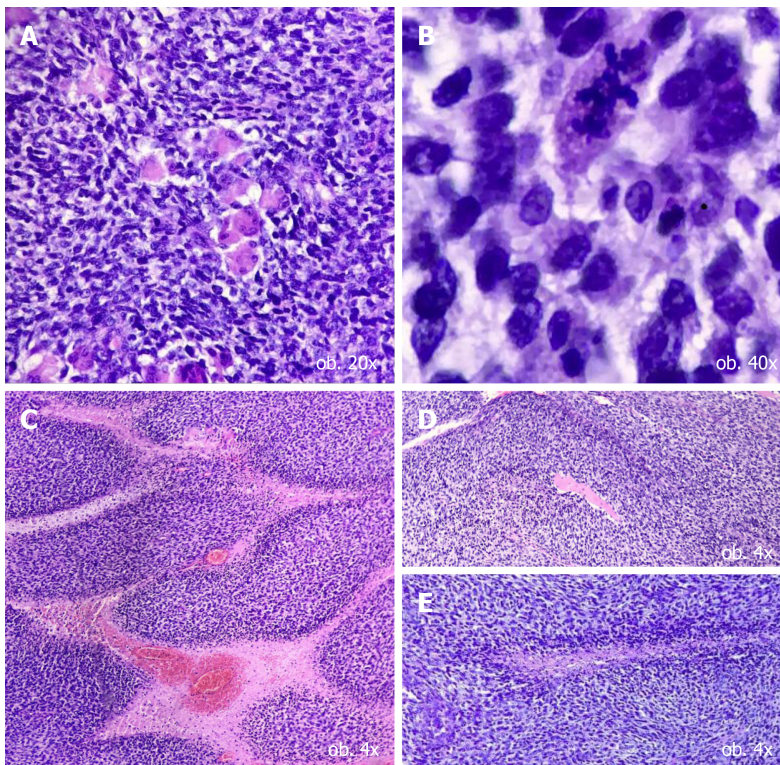


Figure 2 Histological features of a hybrid tumor of the breast. A and B: Major population, some of the cells showing rhabdomyoblastic differentiation (A) and atypical mitoses (B); C-E: Small cell population, demonstrating lobular architecture (C), with formation of rosette-like structures (D and E).

DISCUSSION

To the best of our knowledge, none of the 30 cases of breast RMS, which were previously published in existing English literature^[2], were reported in males, despite the fact that the RMSs with other localizations, such as those of the head and neck region, are mostly found in men^[6,7].

Although the RMS is a relatively classic malignancy, which can be identified by an experienced pathologist with Haematoxylin-Eosin and only confirmed by the immunohistochemical stains, its rare variants might induce challenges in daily practice. The most common histologic variants of RMS are the embryonal-, botryoid-, alveolar- and pleomorphic subtype^[7,8], the latter also being the predominant component of our case. For the diagnosis of sarcomas with dual components, it is mandatory that the histological examination of tumour cells be completed by a large panel of immunohistochemical markers. It is necessary to rule out carcinomas, melanomas, lymphomas and other tumours with neural origin or neuroendocrine differentiation (Table 2).

As regards the genesis of RMS with dual components, it is known that during embryonic myogenesis^[4,9-11], myoblasts become mitotically active, then they fuse to form myotubes, which are large elongated cells with abundant eosinophilic cytoplasm. These large cells form primordium of skeletal muscle fibres and can remain in different stages of development, being the key elements of a further malignant tumour^[4,9-11]. In our case, within the predominant tumour component, large cells resemble the rhabdomyoblasts, which are formed in the early embryologic stage of myogenesis, with some of them also showing multinucleated aggregates.

Our case is of great interest, especially due to the presence of a second, minor cell population resembling MEM, besides the rhabdomyomatous differentiation. MEM, primarily known as gangliorhabdomyosarcoma, is defined as a mixed malignant tumour, one of the elements of which is the RMS component^[8,9]. It is included within the group of tumours with neuroectodermal differentiation, together with PNET/Ewing sarcomas. This tumour is an exceptional finding, as most of the previously reported cases were diagnosed in children^[8,12,13]. The case described in this article was firstly diagnosed as a malignant tumour with neural differentiation, due to the predominance of a PNET-like component in the biopsy specimen.

The presence of the MEM component, in this case with an RMS phenotype, could be explained by the plasticity of the tumour cells, which might have allowed

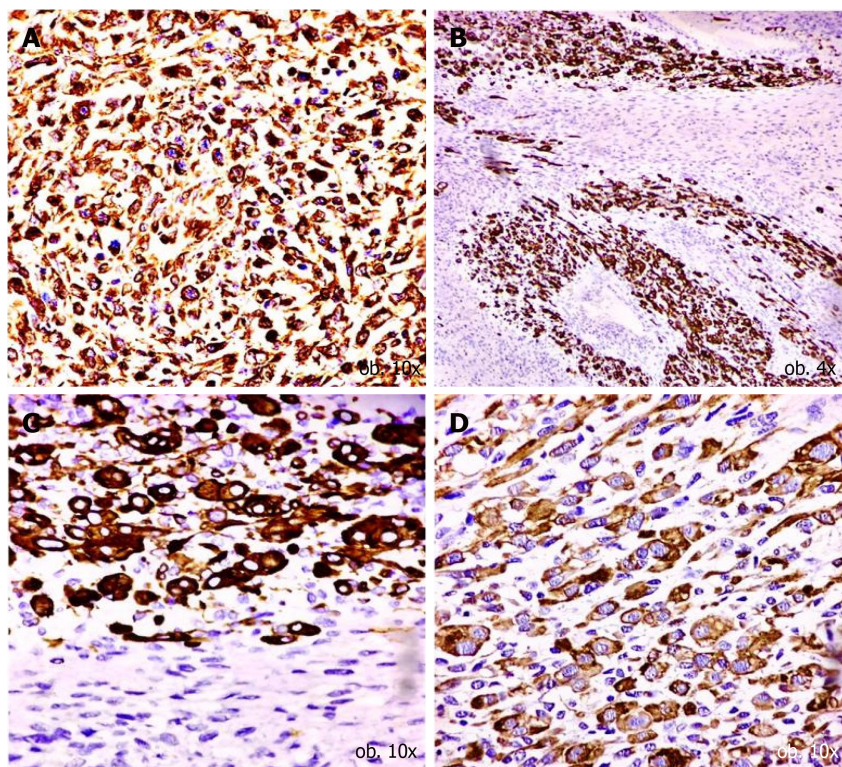


Figure 3 Immunohistochemical profile of major cell population. A: Vimentin diffuse positivity confirms the mesenchymal origin; B-D: The rhabdomyosarcomatous differentiation is confirmed by the positivity for desmin (B), myogenin (C) and sarcomeric actin (D).

dedifferentiation. We have not been able to find any study to support this hypothesis, however, the prevalence of this phenomena, mostly in a young population, along with a first diagnosis of pure RMS, may be two plausible arguments which strengthen this theory^[14,15]. Hence, further studies are needed to confirm/infirm this hypothesis. Another drawback is the lack of a complete microscopic analysis of the tumour mass, as can occur in biopsy specimens. In our case, besides the presence of small CD99 positive cells, admixed within a larger one, another indicator of a second component was the presence of Homer-Wright-like rosettes, composed of circular strands of tumour cells with round-oval nuclei, surrounding fibrillary cores. These are mostly characteristic of tumours with neural or ectodermal origins, as in cases of PNET^[13].

Thus, in this case, the diagnosis was RMS with neuroectodermal differentiation. Besides the arguments favouring this diagnosis, there is a further hypothesis related to the specific topography of the tumour. Breast embryogenesis is intimately related to the presence of milk lines^[16]. These structures emerge from its primordium, known as the mammary ridge, which represents microscopic thickenings of the ectodermal layer of the embryo. These start as microscopic conglomerates of ectodermic cells which migrate from the caudal region proximally, to their final location and to fully develop the mammary glands^[13,16]. Taking into account these embryogenetic particularities, neuroectodermal differentiation can be present in the sarcomas of the mammary region more frequently than previously thought.

As the diagnosis of MEM is difficult to establish, little is known about its molecular pathways and therapeutic guidelines^[3,8,12,13]. Radiotherapy with/without chemotherapy can be done before or after surgical excision^[17]. Kawamoto *et al*^[18] postulated that the evolution of patients with MEM mainly depends on the resectability of the tumor. These fact is also sustained by the study of Freitas *et al*^[19] who demonstrated that incomplete resection of the tumor, such in the present case, is followed by recurrence even though the patients received chemotherapy too. Regarding the chemotherapeutic regimen, its choice primarily depends on the histologic type of the mesenchymal component of MEM. If the chemotherapy targets the mesenchymal RMS component, radiotherapy targets the second, minor population, with neuroectodermal differentiation. The decision of adding or not radiotherapy belongs to the oncologist and should take into account the extent of the neuroectodermal population. In this case, the irradiation dose can go up to 36-45 Gy^[17]. In cases such as those presented in this paper, therapeutic regimen should be focused on the predominant component, which was the RMS^[4,8,9,17].

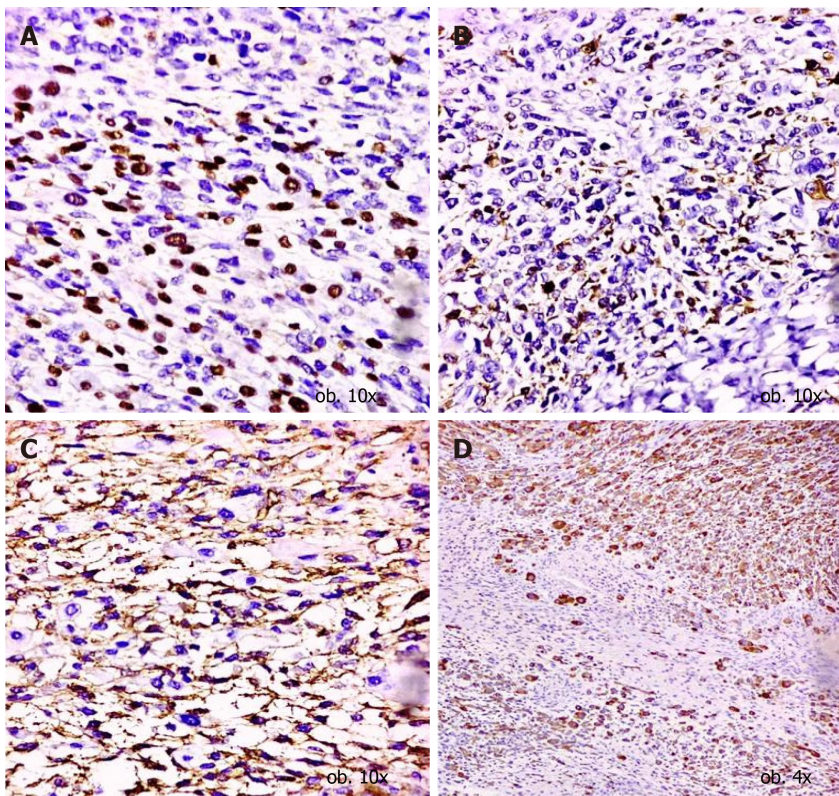


Figure 4 Immunohistochemical profile of small cell population. A-C: The neuroectodermal origin is confirmed by the positivity for neurofilament (A), neuron specific enolase (B) and CD99 (C); D: CD56 positivity proves the interaction between myocytes and neural cells.

We found only two previously published cases of MEM, one by Oppenheimer *et al*^[14] who reported a case of a 17-mo-old boy with MEM of the left wrist, who was disease free, four years after diagnosis. The second case, published by Paikos *et al*^[15] diagnosed a seven-year-old boy with a MEM of the orbit, who had no residual tumour cells after 15 mo of follow-up treatment. This good evolution can be explained by the patient's age, as tumour cells are more chemosensitive when a patient is younger^[14,15], but also by the pure form of these previously reported cases. On the other hand, in our patient, first diagnosis was established three months after occurrence of the tumour (based on the patient's anamnesis) and another six months passed without any therapy, due to the patient's refusal, since distant metastases occurred.

CONCLUSION

This case highlights the heterogeneity of sarcomas, which is not as common as in malignant tumours with epithelial origins. On the other hand, although RMS is known to display very aggressive behaviour, almost one year passed from diagnosis to distant metastases. Such cases, diagnosed at an early stage, might present a better prognosis. However, therapeutic guidelines should be more focused on malignancies with dual components.

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