Dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma in the vulva: a case report

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Summary

Objective: To review the clinical, morphologic, immunohistochemical, and histogenetic characteristics of dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma and explore current treatment options. *Methods:* We describe the case of a 38-year-old patient with a tumor measuring 5.7 cm on the right labium majus of the vulva. Serial sections stained with hematoxylin-eosin were examined and immunohistochemical staining was performed for CD34 and PDGF receptor alpha and beta (PDFGRA and PDGFRB). *Results:* The histologic study showed spindle-cell proliferation typical of dermatofibrosarcoma protuberans and other areas containing fibrosis and giant cells lining pseudovascular spaces. Both tumor areas expressed CD34, PDGFRA, and PDGFRB. *Conclusions*: Only two cases of dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma in the vulva have been reported to date. Both dermatofibrosarcoma protuberans and giant cell fibroblastoma are characterized by the translocation t (17;22) (q22;q13). The fact that PDGFRA and PDGFRB are overexpressed in these tumors opens new treatment options with imatinib. Surgical excision with wide margins or Mohs micrographic surgery continues to be the treatment of choice.

Key words: Dermatofibrosarcoma protuberans; Giant cell fibroblastoma; Imatinib. COL1A1-PDGFB; Mohs micrographic surgery.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue tumor of intermediate-grade malignancy that causes local recurrences but has a low risk of metastasis [1].

The tumor mostly affects the trunk and proximal areas of the limbs [2] and is most common in adults with a peak incidence at 20-40 years of age, although it can occur in children and adolescents [3]. Vulva involvement is rare; only 29 cases have been reported to date [4] and only two of these have occurred in association with giant cell fibroblastoma [5, 6]. Both DFSP and giant cell fibroblastoma contain a translocation between the genes *COL1A1* (17q22) and *PDGFB* (22q13) that results in the formation of a chimeric gene encoding a transforming protein with similar effects to PDGFB, which induces mitogenic stimulation via the activation of the PDGFB receptor (PDGFRB) [7, 8].

The treatment of choice for localized disease is complete excision with wide margins (over 3 cm) or Mohs micrographic surgery [9].

Tumors that overexpress PDGFRB are amenable to treatment with imatinib mesylate, thus opening new treatment options for local recurrences, distant metastases, and difficult-to-access tumors that cannot be completely excised. The drug is also an option for treating children when the alternative is mutilating surgery [10].

Case Report

We report the case of a 38-year-old black female in her 19th week of pregnancy who presented a nodule on the outer genitals that had grown since it had appeared several months earlier. Of note in her history was the removal of a verrucous lesion from the right labium majus three years earlier, for which no report was provided. Examination revealed soft, hyperpigmented, painless depressed plaque measuring approximately 4-5 cm on the right labium majus. The findings of the rest of the examination were consistent with amenorrhea and the abdominal ultrasound showed a live fetus with normal features. The diagnosis following fine-needle aspiration biopsy of the plaque was a mesenchymal tumor without cellular atypia. It was decided to postpone removal of the tumor until after pregnancy. Following a cesarean, the patient was scheduled for excision of the nodule under regional anesthesia. The depressed plaque was seen to be a soft tumor measuring approximately 6 cm with no clear cleavage plane.

A surgical specimen was sent to the pathology department measuring 5.7 x 5 x 2 cm, partially covered by skin, and the resection margins were marked with India ink. Serial sectioning showed a solid tumor of elastic consistency with poorly defined borders that formed whitish bands in the dermis and subcutaneous tissue. Multiple samples were taken for histologic and immunohistochemical analysis.

Sections 4-µm thick were cut from formalin-fixed, paraffin-embedded tissue and stained with hematoxylin eosin. Immunohistochemical staining was performed on sections of paraffin-embedded blocks using the avidin-biotin-peroxidase method using antibodies to the following antigens: CD34 (Dako, Glostrup, Denmark, monoclonal: QBEnd/10, dilution 1:100), muscular actin (Dako, Carpintería Clif. monoclonal: HHF-35, dilution 1:50), desmin (Dako, monoclonal: D33, dilution 1:3000), vimentin (Dako, Glostrup, Denmark, moclonal: V9, dilution 1:100), factor XIIIa (Novocastra, Newcastle. U.K. monoclonal: E-9801, prediluted), C-kit (Dako, Glostrup, Denmark, polyclonal, dilution 1:400), PDGFRA (c-20) (Santa

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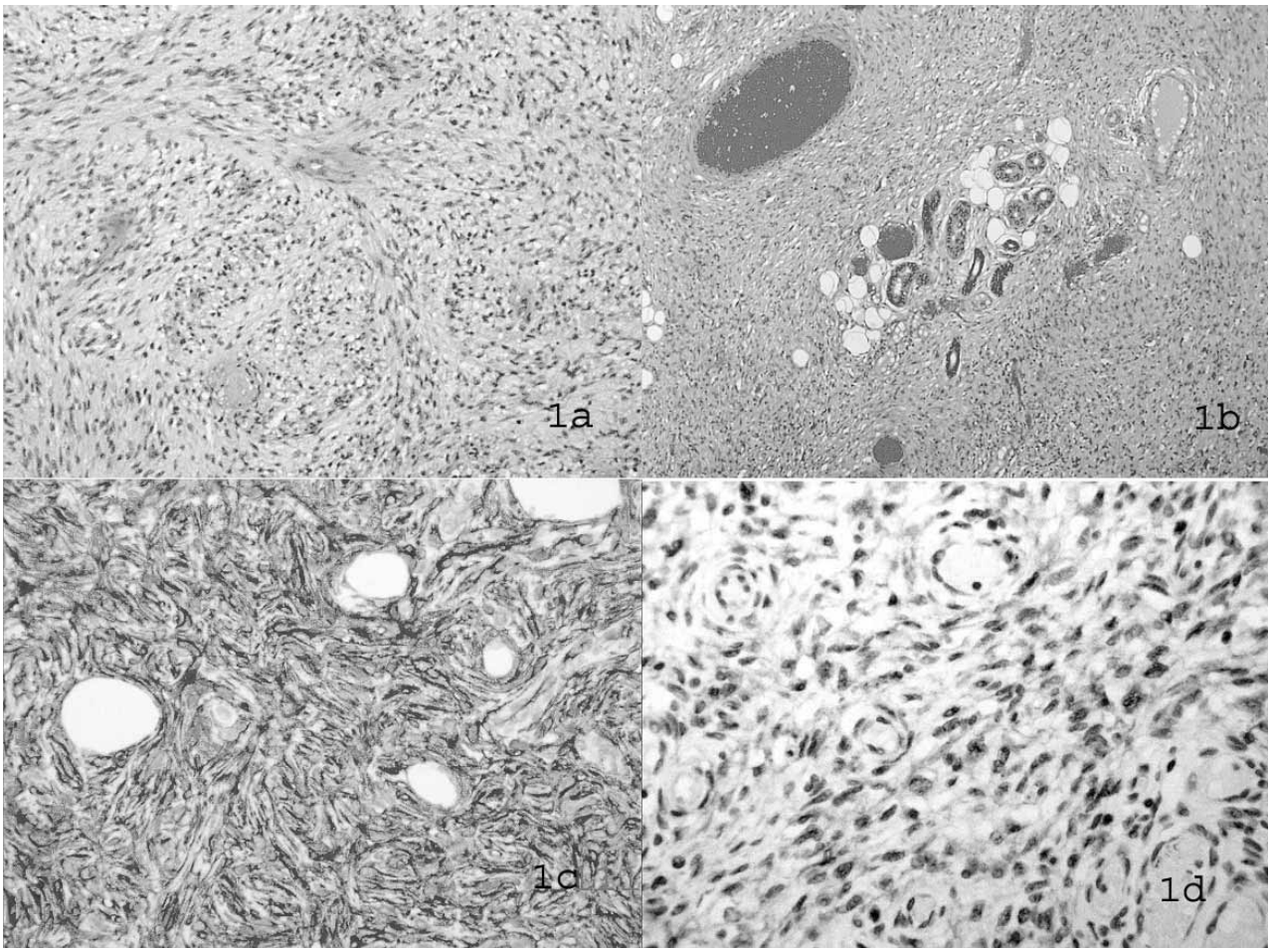

Figure 1. — Dermatofibrosarcoma protuberans. Storiform growth pattern (a); Uniform spindle cells infiltrate among fat cell and adnexal structures (b); Strong diffuse CD34 immunoreactivity (c); Low diffuse PDGFRB immunoreactivity (d).

Cruz Biotechnology USA, polyclonal, dilution 1:200), PDGFRB (p-20) (Santa Cruz Biotechnology USA, polyclonal, dilution 1:200), S-100 (Dako, Glostrup, Denmark, polyclonal, prediluted) and cytokeratin AE-1/AE-3 (Dako, Glostrup, Denmark, monoclonal: AE1/AE3 prediluted). Positive and negative controls were used.

Results

Examination of hematoxylin-eosin stained sections revealed neoplastic proliferation of cells with a mesenchymal appearance containing areas with a storiform growth pattern (Figure 1a) invading the dermis and with extensive infiltration of the subcutaneous tissue, surrounding adnexal structures without destroying them (Figure 1b). The cells were elongated, with scant cytoplasm and large, elongated nuclei with fine chromatin, small but visible nucleoli, and 2 mitoses per 10 high-power fields. In the other areas, the tumor had foci of fibrosis with multinucleated giant cells lining pseudovascular spaces of varying size (Figure 2a). The surgical margins were extensively infiltrated by the lesion.

The tumor cells in both areas of the tumor were positive for CD34 (Figures 1c and 2b), vimentin, PDGFRB (Figures 1d and 2c) and PDGFRA, and negative for the other tumor markers. The diagnosis was dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma.

Mohs micrographic surgery was performed (by three micrographic stages) and free margins were achieved. Defect reconstruction was healed by secundary intention (Figures 3a and 3b). The patient remains relapse-free in follow-up (15 months) (Figure 3c).

Discussion

DFSP rarely presents on the vulva; only 29 such cases have been reported to date [4] and only two of these have occurred in association with areas of giant cell fibroblastoma [5, 6]. The age of the patients described in the literature ranges from 23 to 76 years and the most common tumor site reported is the right labium majus [4]. In our case, the patient was 38 years old and the tumor was on the right labium majus.

In the early stages of disease there are three non-protuberant clinical forms of DFSP [11].

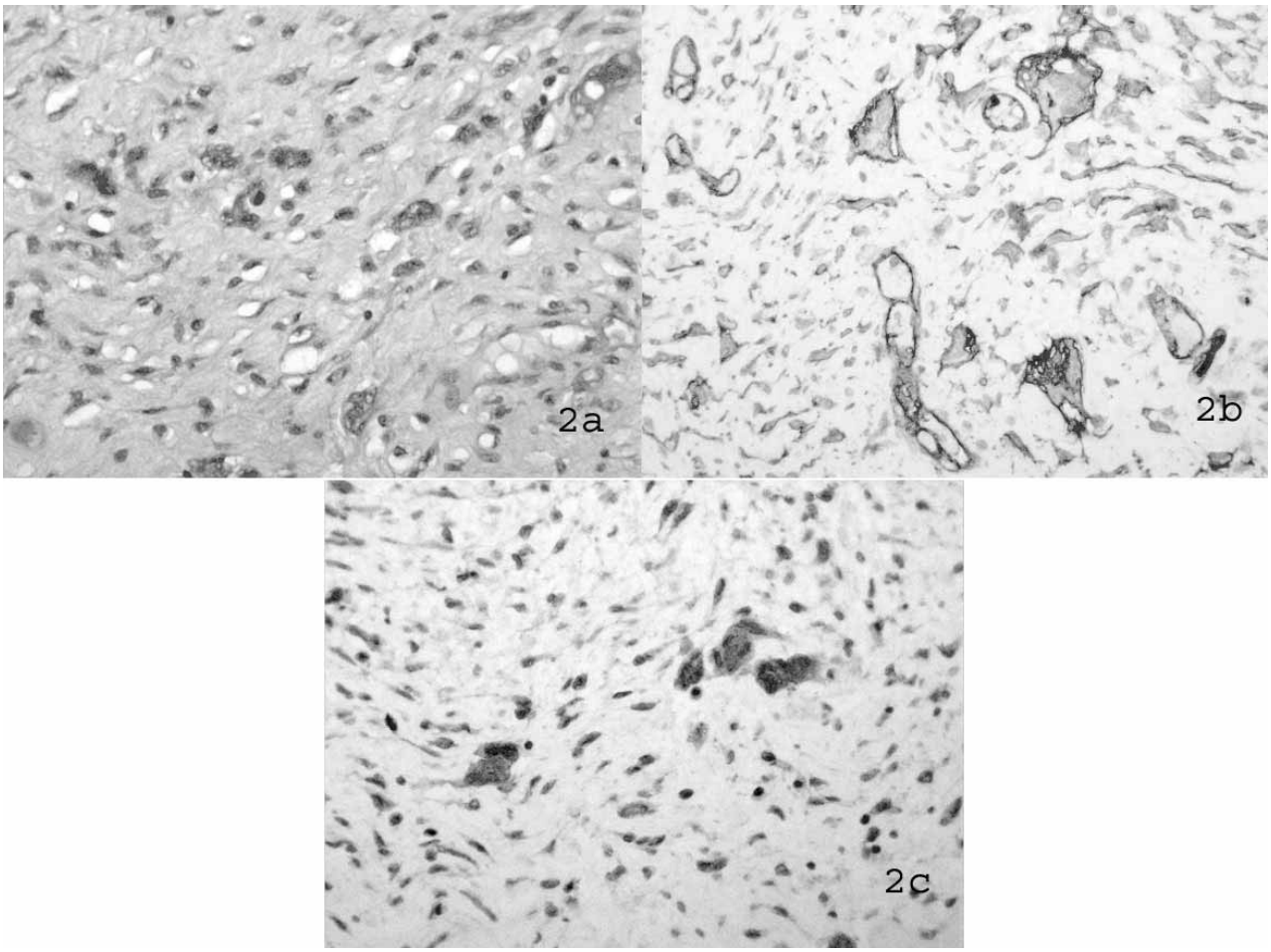

Figure 2. — Giant-cell fibroblastoma area. Pleomorphic giant cell with pseudovascular spaces (a); Strong diffuse CD34 immunoreactivity (b); Low diffuse PDGFRB immunoreactivity (c).

1) A morphea-like form consisting of an indurated white or brown plaque resembling a scar, morphea, morpheaform basal cell carcinoma, or plaque-like dermatofibroma.

2) An atrophoderma-like form consisting of a white or brown soft, depressed plaque.

3) An angioma-like form (the least common type) consisting of a red or violaceous plaque that can be indurated or soft and clinically resembles an angioma.

Although the most common clinical form of DFSP described in the vulva is a vulvar mass [4], our patient had the second type of non-protuberant clinical form. DFSP can also present as a central nodule with satellite nodules. In its early stages, it is an indolent lesion that, with time, develops protruding nodules that can become ulcerative, painful, and also bleed.

CD34 is an important diagnostic aid as it is frequently expressed in DFSP, although it is not specific to this tumor. Factor XIIIa is useful for differentiating DFSP from cellular fibrous histiocytoma (negative in the former and positive in the latter) [1].

Cytogenetic analysis of DFSP has shown the presence of a supernumerary ring chromosome resulting from the translocation t (17; 22) (q22;q13) [12, 13]. Translocation results in the fusion of two genes: collagen type 1 alpha 1 (*COL1A1*) (chromosome 17) and *PDGFB* (chromosome 22). This generates a fusion protein COL1A1-PDGFB that is processed outside the cell until it becomes a fully mature, functional PDGFB protein. When released, PDGFB is capable of inducing mitogenic stimulation via the activation of its receptor. The t (17; 22) translocation product COL1A1-PDGFB thus induces the activation of PDGFRB by autocrine and paracrine production of its functional ligand [14]. In our case, the tumor cells overexpressed both PDGFRA and PDGFRB.

Whether or not trauma is a causative factor in DFSP is a matter of debate. It is possible, that trauma might play a role in the development of this tumor, as in 10-20% of cases there is a history of previous trauma and there have also been reports of dermatofibrosarcoma protuberans on surgical scars, burns, radiodermatitis sites and vaccine injection sites [15, 16]. Our patient had undergone surgery three years earlier (removal of a verrucous lesion from the right labium majus for which no histology report was available).

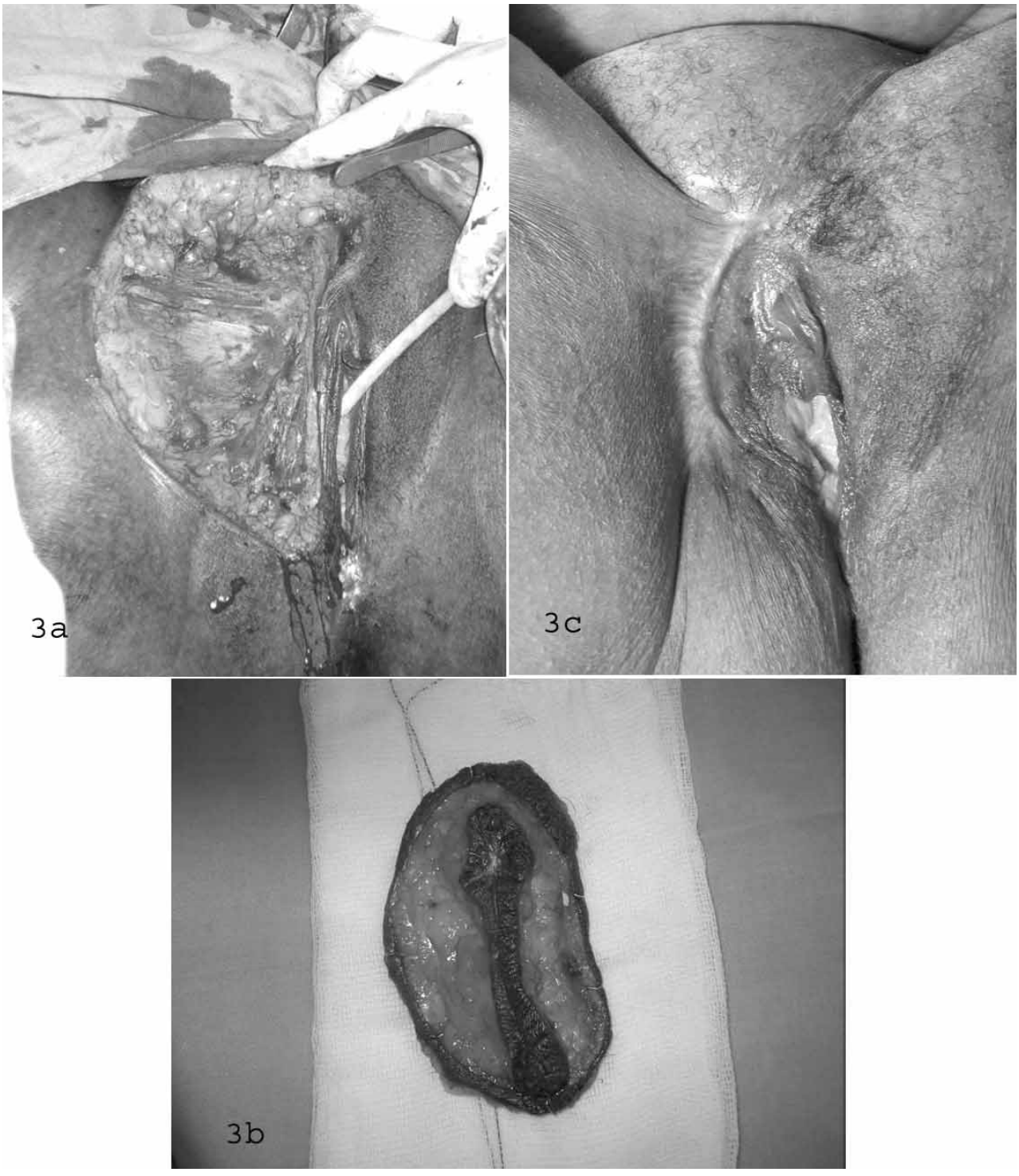

Figure 3. — Mohs micrographic surgery (a-b). Clinical appearance without recidive at 15-month follow-up (c).

DFSP and giant cell fibroblastoma (which is more common in children) [17] are very closely related as they have cytologic and molecular similarities (e.g., they both have the translocation t (17; 22)) [18]. Giant cell fibroblastoma can have areas with a storiform pattern and there have been reports of DFSP with areas of giant cell fibroblastoma, although just two cases have been described in the vulva [5, 6].

In DFSP tumor cells invade the subcutaneous tissue in the form of finger-like projections through the septae and lobules. These projections contain few cells and can initially look like normal fibrous bands. This makes it diffi-

cult to determine the true extent of the lesion and explains why tumors recur after surgery with apparently wide margins.

Localized disease is treated by complete excision, via conventional surgery with wide margins (over 3 cm) or standard Mohs micrographic surgery [9]. Recurrence rates range from 40% with excision margins of 2 cm, 20% with margins of 3 cm, and less than 15% with margins of 5 cm [19]. With Mohs surgery, recurrence rates are less than 5% [20]. Local recurrence is most common in the first three years after surgery [1]. We performed Mohs micrographic surgery with no recurrences to date (15 months).

Metastasis occurs in 0.3-0.5% of patients [12, 21]. In most cases, it occurs after local recurrences, with a mean interval of six years from the first excision. Prognosis is very poor, with a survival time of less than two years from detection of the metastasis.

DFSP tumors express three kinases (c-abl, PDGFRA, and PDGFRB) and are amenable to treatment with imatinib mesylate [4]. Several authors have suggested that imatinib mesylate induces apoptosis in tumor cells, which could destroy the tumor, while others believe that it alters the tumor phenotype, reducing proliferation and consequently tumor size, but not eliminating the tumor completely. The fact that PDGFRA and PDGFRB are expressed in dermatofibrosarcoma protuberans opens new treatment options with imatinib for local recurrences, distant metastasis, difficult-to-access tumors in which complete excision is not possible, and children where the alternative is mutilating surgery [10].

Conclusions

DFSP rarely presents in the vulva. To our knowledge, there have been only 29 cases reported in the literature with only two of them combined with giant cell fibroblastoma. The tumor is a low-grade sarcoma that tends to recur if not excised with wide margins. It is associated with a translocation t (17; 22) between the genes *COL1A1* (17q22) and *PDGFB* (22q13), which results in the formation of a protein with similar effects to PDGFB due to the activation of its receptor, which was found to be overexpressed in our patient. Surgical excision with wide margins or Mohs micrographic surgery continues to be the treatment of choice. The expression of PDGFRB and PDGFRA in DFSP opens new treatment options with imatinib mesylate for patients with recurrent disease, locally advanced disease, and metastasis.

References

[1] Sanmartin O., Llombart B., Lopez-Guerrero J.A., Serra C., Requena C., Guillén C.: "Dermatofibrosarcoma protuberans". *Actas Dermosifiliogr*., 2007, *98,* 77.

[2] Meis-Kindblom J.M., Ezinger F.M.: "Color Atlas of Soft Tissue Tumors". Meis-Kindblom J.M., Ezinger F.M. (eds.). St Louis. Mosby-Wolfe, 1996, 54.

[3] Mckee P.H., Fletcher C.D.: "Dermatofibrosarcoma protuberans presenting in infancy and childhood". *J. Cutan. Pathol*., 1991, *18,* 241.

[4] Edelweiss M., Malpica A.: "Dermatofibrosarcoma protuberans of the vulva: A clinicopathologic and immunohistochemical study of 13 cases". *Am. J. Surg. Pathol*., 2010, *34,* 393.

[5] Kholova I., Ryska A., Dedic K.: "Composite tumor consisting of dermatofibrosarcoma protuberans and giant cell fibroblastoma with intramural endometriosis. Report of a case". *Pathol. Res. Pract*., 2001, *197,* 263.

[6] Gökden N., Dehner L.P., Zhu X., Pfeifer J.D.: "Dermatofibrosarcoma protuberans of the vulva and groin: detection of COL1A1-PDGFB fusion transcripts by RT-PCR". *J. Cutan. Pathol*., 2003, *30*, 190.

[7] O'Brien K.P., Seroussi E., Dal Cin P.D., Sciot R., Mandahl N., Fletcher J.A. *et al*.: "Various regions within the alpha-helical domain of the COL1A1 gene are fused to the second exon of the PDGFB gene in dermatofibrosarcoma and giant-cell fibroblastoma". *Genes Chromosomes Cancer,* 1998, *23,* 187.

[8] Greco A., Fusetti L., Villa R., Sozzi G., Minoletti F., Mauri P. *et al*.: "Transforming activity of the chimeric sequence formed by the fusion of collagen gene COL1A1 and the platelet derived growth factor b-chain gene in dermatofibrosarcoma protuberans". *Oncogene,* 1998, *17*, 1313.

[9] Paradisi A., Abeni D., Rusciani A., Cigna E., Wolter M., Scuderi N. *et al*.: "Dermatofibrosarcoma protuberans: Wide local escisión us. Mohs micrographic sugery". *Cancer Treta Rev.,* 2008, *34,* 728.

[10] McArthur G.A.: "Molecular targeting of dermatofibrosarcoma protuberans: a new approach to a sugical disease". *J. Natl. Compr. Canc. Netw*., 2007, *5*, 557.

[11] Martin L., Piette F., Blanc P., Mortier L., Avril M.F., Delaunay M.M. *et al*.: "Clinical variants of the preprotuberant stage of dermatofibrosarcoma protuberans". *Br. J. Dermatol*., 2005, *153,* 932.

[12] Vanni R., Faa G., Dettori T., Melis G.P., Dumanski J.P., O'Brien K.P.: "A case of dermatofibrosarcoma protuberans of the vulva with a COL1A1/PDGFB fusion identical to a case of giant cell fibroblastoma". *Virchows Arch*., 2000, *437,* 95.

[13] Pedeutour F., Simon M.P., Minoletti F., Sozzi G., Pierotti M.A., Hecht F. *et al*.: "Ring 22 chromosomes in dermatofibrosarcoma protuberans are low-level amplifiers of chromosome 17 and 22 secuences". *Cancer Res*., 1995, *55,* 2400.

[14] Shimizu A., O'Brien K.P., Sjoblom T., Pietras K., Buchdunger E., Collins V.P. *et al*.: "The dermatofibrosarcoma protuberans associated collagen tupe I alpha 1/platelet-derived growth factor (PDGF) B-chain fusion gene generates a transfroeming protein that is processed to PDGF-B". *Cancer Res*., 1999, *59*, 3719.

[15] Taylor H.B., Helwis E.B.: "Dermatofibrosarcoma protuberans. A study of 115 cases". *Cancer,* 1996, *15,* 717.

[16] Gloster H.M. Jr.: "Dermatofibrosarcoma protuberans". *J. Am. Acad. Dermatol*., 1996, *35* (3 pt-1), 355.

[17] Fletcher C.D.: "Giant cell fibroblastoma of soft tissue: a clinicopathological and immunohistochemical study". *Histopathology,* 1988, *13,* 499.

[18] Dal Cin P., Polito P., Van Eyken P., Sciot R., Hernandez J.N., Garcia J.L., Van den Berghe H.: "Anomalies of chromosomas 17 and 22 in giant cell fibroblastoma". *Cancer Genet Cytogenet*., 1997, *97,* 165.

[19] Gloster H.M. Jr., Harris K.R., Roenigk R.K.: "A comparison between Mohs micrographic sugery and wide surgical excision for the treatment of dermatofibrosarcoma protuberans". *J. Am. Acad. Dermatol*., 1996, *35,* 82.

[20] Snow S.N., Gordon E.M., Larson P.D., Bagheri M.M., Bentz M., Sable D.B.: "Dermatofibrosarcoma protuberans: a report on 29 patients treated by Mohs micrographic surgery with long-term follow-up and review of the literature". *Cancer,* 2004, *101,* 28.

[21] Stadler F.J., Scott G.A., Brown M.D.: "Malignant fibrous tumours". *Semin. Cutan. Med. Surg*., 1998, *17,* 141.

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