Lung Metastasis From Fibrosarcomatous Dermatofibrosarcoma Protuberans of the Vulva: A Rare Case Report

Ioannis Athanasios Vathiotis, MD,[1] Eleni Psichogiou, MD,[2] Konstantinos Nikolaos Syrigos, MD, PhD,[1] and Elias Alexandros Kotteas, MD, PhD[1]

Key Words: dermatofibrosarcoma, DFSP, FS DFSP, vulva, metastatic

(*J Low Genit Tract Dis* 2018;22: 85–87)

Dermatofibrosarcoma protuberans (DFSP) is a rare, low-grade, soft tissue sarcoma arising in the dermis. It accounts for 0.1% of all cancers and 1% of all soft tissue sarcomas,[1] with an estimated incidence of 0.8 to 4.2 cases per million persons per year, gradually increasing over time.[2,3] Vulva represents an uncommon primary site for this mesenchymal neoplasm, as sarcomas comprise 1.8% to 3% of all vulvar malignant tumors.[4] Presence of atypia, increased mitotic rates, necroses as well as distinct immunohistochemical patterns delineate fibrosarcomatous transformation, an intermediate- to high-grade sarcoma that appears in 5% to 15% of cases, with implications concerning tumor prognosis. Current treatment modalities have recently changed with the identification of t(17;22)(q22;q13) reciprocal translocation, present in most cases.[5] We herein report the second case of metastatic vulvar fiborsarcomatous DFSP (FS-DFSP) and eventually summarize current literature on this specific topic, focusing on the pivotal role of genetic testing in the correct choice of treatment for patients experiencing metastatic disease.

CASE PRESENTATION

A 72-year-old postmenopausal woman presented to outpatient clinic for evaluation of worsening chest pain on her right hemithorax and productive cough during the last 2 months. Her personal history was significant for breast cancer, multiple venous thromboembolic events, and radical vulvectomy surgery for twice locally recurrent FS-DFSP of the vulva. The FS-DFSP initially presented as a "protuberant" skin lesion on the right labium majus and was treated with local excision 4 years ago. Histopathological examination of the resection specimen revealed positive surgical margins. The lesion recurred in a period of 18 months and wide local excision (WLE) with negative resection margins followed. Five months later, after the second local recurrence, radical vulvectomy surgery was elected. She was an active smoker and her family history was insignificant.

Her vital signs were within normal limits and her performance status according to Eastern Cooperative Oncology Group scale was 1. Physical examination revealed diffuse expiratory rhonchi on auscultation of both lungs but no signs of regional recurrence during examination of the external genitalia. Chest radiography showed bilateral pulmonary nodules and high-resolution computed tomography (CT) of the chest that followed exhibited multiple nodules and masses of varying sizes in both lungs, as well as enlarged right and left hilar and mediastinal lymph nodes. Both brain and abdominal CT scans were normal. Blood and urine investigations were also normal. The patient underwent fine needle biopsy under CT guidance of the larger mass in the right lower lobe for the histologic identification of the lesions.

Histopathological examination unveiled diffuse infiltration of the lung parenchyma by fascicles of spindle cells mutually intertwined or arranged in a storiform pattern and radially around vasculature. Immunohistochemical analysis demonstrated tumor cells that were positive for CD34 and vimentin. Some cells stained also positively for CD10 antigen. Ki67 showed up to 30% positivity focally (see Figure 1). The previous findings were suggestive for lung metastasis of FS-DFSP.

Fluorescence in situ hybridization test that followed on the tissue obtained by fine needle biopsy was positive for t(17;22)(q22;q13) fusion gene. Patient did not have any contraindications to imatinib administration. Oral imatinib was, therefore, initiated at a dose of 400 mg twice daily. Patient is currently on treatment exhibiting clinical improvement at 4 weeks. Grade 2 edema of the lower limbs (10%–30% interlimb discrepancy in volume or circumference at point of greatest visible difference) as well as grade 1 diarrhea (increase of <4 stools per day over baseline) appeared during the third week of treatment.

DISCUSSION

Although DFSP has been linked to previous skin trauma, its cause remains obscure. Recent studies have delineated the presence of t(17;22)(q22;q13) reciprocal translocation in approximately nine of ten patients experiencing the disease. Genomic gains of the fusion COL1A1-PDGFβ gene, microsatellite instability, and p53 mutations all compose genomic features commonly acquired within areas of fibrosarcomatous transformation. Molecular mechanisms implicated in the pathogenesis of t(17;22) negative DFSP, accounting for 10% of cases, are not yet fully understood and constitute a field of active investigation.[5]

Dermatofibrosarcoma protuberans most frequently presents on the trunk (40%–50%), followed by the proximal extremities (30%–40%) and the head and neck (10%–15%).[5] Vulva represents an uncommon primary site for this tumor, with less than 50 cases reported in English literature[6]; Table 1 summarizes all cases of vulvar FS-DFSP reported until today. Dermatofibrosarcoma protuberans is more common among blacks. In addition, some studies indicate a scarce male predominance. Although it has been recorded in children as well as adults of all ages, it usually appears in middle age patients.[5]

Typically, it arises as a pink to red-bluish, tardy growing, sclerotic plaque-like lesion. Telangiectasias or small satellite nodules may be spotted on the periphery. During its initial latent period lasting for months to years, DFSP is confined to the dermis spreading laterally. Although it rests fixed to the overlying skin, it remains mobile on palpation because deeper structures are not yet involved. The subsequent accelerated growth phase is marked

[1]Oncology Unit, Sotiria General Hospital, University of Athens, Athens, Greece; and [2]Department of Pathology, Sotiria General Hospital, University of Athens, Athens, Greece

Reprint requests to: Elias Kotteas, MD, PhD, Sotiria General Hospital, University of Athens, 152 Mesogeion Avenue, 11527, Athens, Greece. E-mail: ilkotteas@med.uoa.gr

The authors have declared they have no conflicts of interest.

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

© 2017, American Society for Colposcopy and Cervical Pathology

DOI: 10.1097/LGT.0000000000000360

Copyright © 2017 American Society for Colposcopy and Cervical Pathology. Unauthorized reproduction of this article is prohibited.

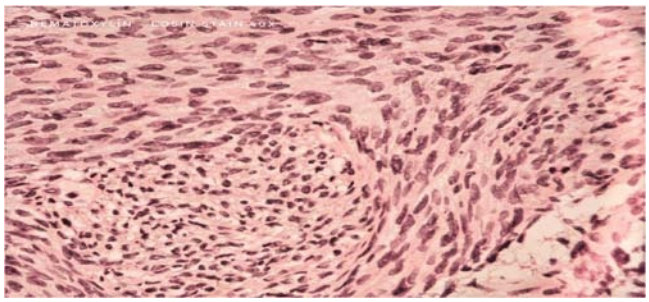

FIGURE 1. Fibrosarcomatous dermatofibrosarcoma protuberans. Fine needle biopsy of the lung, stains hematoxylin and eosin: Spindle cells in a storiform pattern, distributed around blood vessels. Ki67, inequally distributed nuclear positivity up to 30%. CD34+, vimentin+, and CD10+.

by vertical infiltration and fixation to subcutis and underlying tissues. Peripheral nodules merge to form a bulkier mass with the classic "protuberant" appearance. Ulceration along with bleeding serves as late events to the natural history of the disease. Dermatofibrosarcoma protuberans usually remains asymptomatic, ranging from 2 cm in new lesions to more than 30 in slighted cases. Tumor-related cachexia is rare even in neglected cases.[10]

The tumor is composed of a monomorphous population of slender spindle cells displaying minimal cytological atypia and meager mitotic activity (typically <5 mitoses in 10 high-power fields), surrounded by a collagenous stroma. It is those cells that are distributed around blood vessels in the storiform or cartwheel pattern, characteristic of this low-grade sarcoma. As the tumor progresses vertically, it penetrates into subcutaneous fat, entrapping lipocytes into a characteristic "honeycomb" or lace-like pattern. The presence of a Grenz zone separating the tumor from the overlying normal epidermis constitutes another histological feature of DFSP. Immunohistochemical staining reveals diffuse and intense positivity for CD34, which is considered a quite sensitive but not fairly specific marker for DFSP, and vimentin. Apolipoprotein D is also regarded as a sensitive marker with applications not only in the diagnosis of DFSP but also in its differential from benign fibrous histiocytoma. Fiborsarcomatous DFSP involves areas within the tumor that have acquired fibrosarcomatous transformation, representing an intermediate- to high-grade sarcoma. The previously mentioned regions contain elevated numbers of spindle cells that display cytological atypia and higher mitotic rates (>10 mitoses in 10 high-power fields) in comparison with classic DFSP. The existence of necroses represents yet another discrepancy of the fibrosarcomatous subtype. CD34 positivity also declines, serving as a useful hint for its differential.[11] In our case, tumor cells stained positively both for CD34 and vimentin.

Complete surgical resection is the backbone of treatment for localized disease. Because the main tumor may send out numerous finger-like projections, its actual size can stretch out four times the clinically involved area. Inability to eradicate the previously mentioned projections, resulting in residual tumor burden, causes disease recurrence.[10] Historically, conservative margin local excision practices have led to recurrence rates as high as 60%.[12] Radical surgical resection can be accomplished with WLE, in which surgical margins obtained extend 3 to 5 cm laterally and deep from the clinically overt lesion, involving the underlying fascia. Nevertheless, when performed, WLE bears an increased risk of complications, along with suboptimal cosmetic results. Alternatively, disease-free surgical margins can be obtained by the use of Mohs micrographic surgery (MMS). Reviewing pooled literature data revealed six DFSP recurrences in 463 patients treated with MMS (1.3%, 95% CI = 0.5%–2.8%), versus 288 recurrences in 1394 WLE cases (20.7%, 95% CI = 18.6%–22.9%), resulting in a 15.9 (95% CI = 7.2–35.5) relative risk of recurrence for WLE surgery, in comparison with resection by MMS.[13] Mohs micrographic surgery is therefore favored, when feasible, as procedure of choice,

TABLE 1. Summary of Vulvar FS-DFSP Cases Reported in Literature

Authors	Age	Location	Initial treatment	Local recurrence	Metastasis	Follow-up
Hammonds et al.[7]	58	NA	Local excision	NA	NA	NA
Hammonds et al.[7]	61	Right labium majus	Local excision with positive margins	One	No	Right radical hemivulvectomy, 18 mo free of disease
Hammonds et al.[7]	44	Left labium majus plus vulva "skin tag"	Local excision with positive margins, WLE 1 mo later.	No	No	6 mo free of disease
Bernárdez et al.[8]	39	Left labium majus	Local excision with positive margins, adjuvant radiotherapy	No	No	12 mo free of disease
Edelweiss et al.[9]	76	Right labium majus plus crural fold mass	WLE with negative margins	Five	Chest wall, hip, and thigh	Dead of disease
Edelweiss et al.[9]	44	Left labium majus	WLE with negative margins	No	No	53 mo free of disease
Edelweiss et al.[9]	23	Right labium majus	WLE with negative margins	No	No	2 mo free of disease
This case	72	Right labium majus	Local excision with positive margins	Two	Lung	Clinical improvement at 1 mo

FS-DFSP indicates fibrosarcomatous dermatofibrosarcoma protuberans; NA, not available; WLE, wide local excision.

© 2017, American Society for Colposcopy and Cervical Pathology

Copyright © 2017 American Society for Colposcopy and Cervical Pathology. Unauthorized reproduction of this article is prohibited.

for radical surgical resection of the primary lesion. Sentinel lymph node biopsy is indicated in FS-DFSP cases.[14] Adjuvant radiotherapy is recommended after initial surgical excision with close or positive margins when repeat surgery cannot be accomplished or in case of fibrosarcomatous subtype no matter margin positivity.[5] Radiation therapy has also been administered as primary therapy in patients with unresectable disease, especially after local relapse.[15]

Current National Comprehensive Cancer Network guidelines recommend imatinib prescription at a dose of 400 mg twice daily, for patients experiencing metastatic DFSP, tested positive for the translocation t(17;22). In the neoadjuvant setting, although imatinib administration is not routine, its use should be considered in borderline resectable cases, before proceeding to surgery. Patients negative for t(17;22) translocation, as well as those who develop imatinib resistance, may benefit from sorafenib or sunitinib administration, both requiring further investigation to confirm matters of efficacy in such cases. Finally, tumors exhibiting fibrosarcomatous transformation quickly develop resistance to imatinib and should be eventually switched to classic anthracycline-based regimens, given the aggressive nature of this specific variant.[5] In our patient, detection of t(17;22) translocation by fluorescence in situ hybridization resulted in imatinib prescription.

Dermatofibrosarcoma protuberans has a tendency to regress; local recurrence rates vary from 20% to 50%, with a median time to recurrence of 32 months. Surgical margins obtained during the initial surgical excision have been established as the most important risk factor for local relapse, because close (<2 cm) resection margins exhibit a statistically significant association with higher rates of recurrence. Fibrosarcomatous transformation, representing an additional risk factor, has been correlated with recurrence rates as high as 58%.[11] The head and neck are identified as the primary sites displaying the highest local recurrence rate, because both the challenging anatomical structures involved and the desired cosmetic result prevent wide excision procedures. Multiple local relapses, older age (>50 years), along with increased cellularity and mitotic rates also constitute additional negative prognostic factors.[14] Metastasis rarely occurs, recorded in 1% to 5.7% of DFSP cases.[16,17] Most common sites involved are the lungs, regional lymph nodes, and bones. Metastatic spreading is more frequent in fibrosarcomatous subtype, appearing in up to 28% of cases.[16]

CONCLUSIONS

Vulva represents an infrequent primary site for DFSP. Occasionally, fibrosarcomatous transformation occurs posing a therapeutic challenge, because of the need of combining disease-free resection margins in respect to oncologic surgical principles with maximum preservation of healthy tissue required for optimal cosmetic results. Furthermore, recent introduction of imatinib in the treatment algorithm has broadened therapeutic options, particularly for patients experiencing metastatic disease. Nowadays, efforts should be directed toward reducing the rates of misdiagnosis, involving all subspecialties required in the treatment of such patients and further exploring therapeutic alternatives for t(17;22) negative cases.

REFERENCES

1. Llombart B, Serra-Guillén C, Monteagudo C, et al. Dermatofibrosarcoma protuberans: a comprehensive review and update on diagnosis and management. *Semin Diagn Pathol* 2013;30:13–28.
2. Simon MP, Navarro M, Roux D, et al. Structural and functional analysis of a chimeric protein COL1A1-PDGFB generated by the translocation t(17;22)(q22;q13.1) in Dermatofibrosarcoma protuberans (DP). *Oncogene* 2001; 20:2965–75.
3. Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. *J Am Acad Dermatol* 2007;56:968–73.
4. Agress R, Figge DC, Tamimi H, et al. Dermatofibrosarcoma protuberans of the vulva. *Gynecol Oncol* 1983;16:288–91.
5. Noujaim J, Thway K, Fisher C, et al. Dermatofibrosarcoma protuberans: from translocation to targeted therapy. *Cancer Biol Med* 2015;12:375–84.
6. Al Tarakji M, Toro A, Di Carlo I, et al. Unusual presentation of dermatofibrosarcoma protuberans in a male patient's breast: a case report and review of the literature. *World J Surg Oncol* 2015;13:158.
7. Hammonds LM, Hendi A. Dermatofibrosarcoma protuberans of the vulva treated using mohs micrographic surgery. *Dermatol Surg* 2010;36: 558–63.
8. Bernárdez C, Machan S, Molina-Ruiz AM, et al. Dermatofibrosarcoma protuberans of the vulva with myoid differentiation. *Am J Dermatopathol* 2015;37:e107–11.
9. Edelweiss M, Malpica A. Dermatofibrosarcoma protuberans of the vulva: a clinicopathologic and immunohistochemical study of 13 cases. *Am J Surg Pathol* 2010;34:393–400.
10. Laskin WB. Dermatofibrosarcoma protuberans. *CA Cancer J Clin* 1992; 42:116–25.
11. Mentzel T, Beham A, Katenkamp D, et al. Fibrosarcomatous ("high-grade") dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. *Am J Surg Pathol* 1998;22:576–87.
12. Rutgers EJ, Kroon BB, Albus-Lutter CE, et al. Dermatofibrosarcoma protuberans: treatment and prognosis. *Eur J Surg Oncol* 1992;18:241–8.
13. Paradisi A, Abeni D, Rusciani A, et al. Dermatofibrosarcoma protuberans: wide local excision vs. Mohs micrographic surgery. *Cancer Treat Rev* 2008;34:728–36.
14. Angouridakis N, Kafas P, Jerjes W, et al. Dermatofibrosarcoma protuberans with fibrosarcomatous transformation of the head and neck. *Head Neck Oncol* 2011;3:5.
15. Haas RL, Keus RB, Loftus BM, et al. The role of radiotherapy in the local management of dermatofibrosarcoma protuberans. Soft Tissue Tumours Working Group. *Eur J Cancer* 1997;33:1055–60.
16. Bowne WB, Antonescu CR, Leung DH, et al. Dermatofibrosarcoma protuberans: a clinicopathologic analysis of patients treated and followed at a single institution. *Cancer* 2000;88:2711–20.
17. Das Gupta TK. *Tumors of soft tissues*. Norwalk, CT: Appleton-Century-Crofts; 1983:396–452.

© 2017, American Society for Colposcopy and Cervical Pathology

Copyright © 2017 American Society for Colposcopy and Cervical Pathology. Unauthorized reproduction of this article is prohibited.