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Dermatofibrosarcoma Protuberans: Retrospective Single Center Analysis Over 16 Years

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Abstract

Dermatofibrosarcoma protuberans (DFSP) is rare mesenchymal neoplasia with a high risk of local recurrence but a low risk of metastatic spread. Tumor cells express CD34 and show a characteristic translocation t(17;22)(q22;q13). We analysed the documented cases at the Department of Dermatology and Allergology between 08/2001 and 08/2017. The diagnosis had been confirmed by histology and immunohistology in all cases. We identified four adults and a pediatric patient with DFSP. All patients were treated by wide surgical excision and controlled by three-dimensional histologic margin control. We observed no recurrence and no metastatic spread. We discuss prognostic factors and emerging treatments.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is rare mesenchymal neoplasia of skin and soft tissue. Most cases develop on trunk and extremities as nodules or plaques, sometimes hyperpigmented. The hyperpigmented type is also known as Bednar a tumour. There is a wide age range, although incidence shows a peak between the second and fifth decade of life.

Diagnosis is made by histology, immunohistology and cytogenetic analysis [1].

DFSP is characterised by a relatively high risk of local recurrence but low risk of metastatic spread. In most cases, a chromosomal translocation can be found: t(17;22)(q22;q13). Thereby, the genes *COL1A1* and platelet-derived growth factor (PDGF)-beta fuse. This leads to an autocrine stimulation loop involving PDGF-beta and PDGF-beta receptor [2].

We analysed our files for DFSP-patients, treatment, and outcome and discussed emerging treatments.

Material and Methods

We analysed the files of the Department of

Dermatology and Allergology, Academic Teaching Hospital Dresden during a 16-year period, i.e. 08/2001 to 08/2017. Demographics, tumour characteristics, treatment and outcome, were investigated.

Results

We were able to identify five patients with a histologically confirmed diagnosis of DFSP. Maximal tumour diameter was between 2 and 4 cm. All tumours were staged T1(≤ 5 cm of tumour diameter on trunk and extremities), N0, M0, G1 (low grade). All tumours were ordinary DFSP without fibrosarcomatous transformation. One tumour was hyperpigmented (Bednar type).

The youngest patient was a 10-year-old girl with a rapidly growing, painless nodule of the chest (Fig. 1). A diagnostic skin biopsy was taken, that revealed large uniform spindle cells reactive with CD34 but negative for S100. Several mitoses were noted. The proliferative fraction as measured by Ki67-reactivity was 1%. A tumour was removed by wide surgical excision with 2 cm safety margin and complete removal of soft tissue down to the muscle fascia by slow Mohs technique. 3-dimensional histologic margin control was performed. The resulting defect was closed by tissue advancement flap after wide subcutaneous mobilisation of wound margins. Healing was uneventful. The 5-year follow-up was relapse-free.

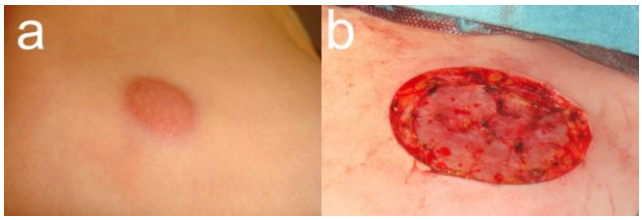

Figure 1: Juvenile dermatofibrosarcoma protuberans on the chest of a 10-year-old girl. (a) Clinical presentation of a well-circumscribed plaque; (b) Defect after wide excision

The remaining patients were adults aged 24, 27, 43, and 61 years of age. The sex ratio for the adult patients was 1:1. One female patient was referred with a recurrence after first surgery elsewhere. The localisation was a shoulder, hip, epigastrium and under belly (Fig. 2).

The safety margins were 1 – 4 cm according to German guidelines [3][4]. In all patients, tumour-free margins were documented. In 4 of five tumours, only one surgical session was necessary, in a single tumour two sessions were needed to obtain tumour-free margins.

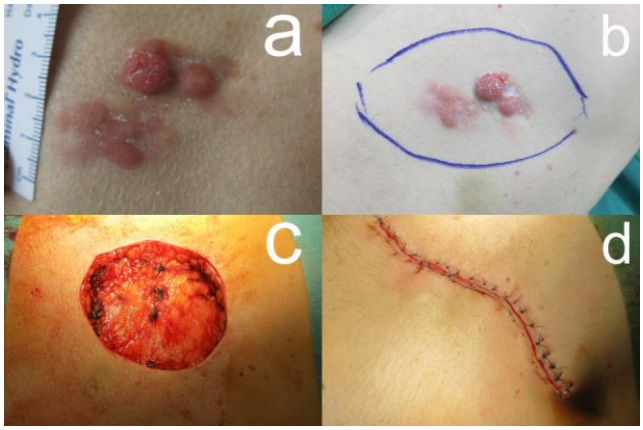

Figure 2: Nodular dermatofibrosarcoma protuberans on the underbelly of a 61-year-old male patient. (a) Clinical presentation; (b) Safety margins; (c) Defect after wide excision; (d) Defect closure by tissue advancement

Tumor cells were positive for CD34 but negative for S100, desmin, pan-cytokeratin, epithelial membrane antigen, and actin. The proliferative index was 1% to 10% measured by Ki67 reactivity. Tumor staging excluded metastatic spread.

Defect closure could be realised by tissue advancement flaps; no grafts were needed. During follow up of up to 7 years neither recurrence nor metastasis was noted.

Discussion

DFSP is rare mesenchymal neoplasia composed of CD34-positive spindle cells. The incidence of this tumour has been estimated between 0.4 and 4.1 patients per million person-years [5][6][7]. The 10-year survival is 99.1%. Negative factors for the unfortunate outcome are higher age, male sex, black race, and anatomic location of the limbs and head [7][8].

Recently, fibrosarcomatous differentiation has been identified as a risk factor for local recurrence [9]. The transformation also increases the rate of metastasis (risk ratio 5.5) and death from disease (risk ratio 6.2) [10]. The fibrosarcomatous transformation is accompanied by an activation of the Akt-mTOR signalling pathway [11]. Treatment of choice is wide tumour excision. Safety margins of 2 cm had a recurrence rate of 1% [12][13][14]. Patients treated with classic or slow Mohs technique have significantly lower recurrence rates [15][16].

DFSP is unresponsive to classical chemotherapy. PDGF-beta, KIT and Abelson murine leukaemia viral oncogene homolog 1 (ABL) inhibitor imatinib mesylate achieved an objective response rate of about 50% in DFSP [17]. In metastatic disease,

imatinib mesylate resulted in median survival progression of ≥ 19 months. The fibrosarcomatous transformation had a less favourable outcome [18][20]. Emerging new drug therapies for advanced or metastatic DFSP are multikinase inhibitors pazopanib [21] and regorafenib [22].

References

1. Steimle-Grauer SA, Hein R. Cutaneous sarcomas. J Dtsch Dermatol Ges. 2017; 15(6):630-648. https://doi.org/10.1111/ddg.13249 PMid:28591457

2. Bichakjian CK, Olencki T, Alam M, Andersen JS, Berg D, Bowen GM, Cheney RT, Daniels GA, Glass LF, Grekin RC, Grossman K, Ho AL, Lewis KD, Lydiatt DD, Morrison WH, Nehal KS, Nelson KC, Nghiem P, Perlis CS, Shaha AR, Thorstad WL, Tuli M, Urist MM, Wang TS, Werchniak AE, Wong SL, Zic JA, McMillian N, Hoffman K, Ho M. Dermatofibrosarcoma protuberans, version 1.2014. J Natl Compr Canc Netw. 2014; 12(6):863-868. https://doi.org/10.6004/jnccn.2014.0081 PMid:24925197

3. Breuninger H, Sebastian G, Garbe C. [Brief guidelines--dermatofibrosarcoma protuberans]. J Dtsch Dermatol Ges. 2006; 4(8):684-5. https://doi.org/10.1111/j.1610-0387.2006.05893.x PMid:16895571

4. Ugurel S, Kortmann RD, Mohr P, Mentzel T, Garbe C, Breuninger H. Brief S2k guidelines-Dermatofibrosarcoma protuberans. J Dtsch Dermatol Ges. 2013; 119(Suppl 3):16-8;17-9.

5. Tolkachjov SN, Schmitt AR, Muzic JG, Weaver AL, Baum CL. Incidence and clinical features of rare cutaneous malignancies in Olmsted County, Minnesota, 2000 to 2010. Dermatol Surg. 2017; 43(1):116-124. https://doi.org/10.1097/DSS.0000000000000936 PMid:28027201 PMCid:PMC5730059

6. Rubio GA, Alvarado A, Gerth DJ, Tashiro J, Thaller SR. Incidence and outcomes of dermatofibrosarcoma protuberans in the US pediatric population. J Craniofac Surg. 2017; 28(1):182-184. https://doi.org/10.1097/SCS.0000000000003203 PMid:27922973

7. Kreicher KL, Kurlander DE, Gittleman HR, Barnholtz-Sloan JS, Bordeaux JS. Incidence and survival of primary dermatofibrosarcoma protuberans in the United States. Dermatol Surg. 2016; 42(Suppl 1):S24-31. https://doi.org/10.1097/DSS.0000000000000300 PMid:26730971

8. Criscito MC, Martires KJ, Stein JA. Prognostic factors, treatment, and survival in dermatofibrosarcoma protuberans. JAMA Dermatol. 2016; 152(12):1365-1371. https://doi.org/10.1001/jamadermatol.2016.1886 PMid:27262160

9. Li Y, Wang C, Xiang B, Chen S, Li L, Ji Y. Clinical features, pathological findings and treatment of recurrent dermatofibrosarcoma protuberans. J Cancer. 2017; 8(7):1319-1323. https://doi.org/10.7150/jca.17988 PMid:28607608 PMCid:PMC5463448

10. Liang CA, Jambusaria-Pahlajani A, Karia PS, Elenitsas R, Zhang PD, Schmults CD. A systematic review of outcome data for dermatofibrosarcoma protuberans with and without fibrosarcomatous change. J Am Acad Dermatol. 2014; 71(4):781-6. https://doi.org/10.1016/j.jaad.2014.03.018 PMid:24755121

11. Hiraki-Hotokebuchi Y, Yamada Y, Kohashi K, Yamamoto H, Endo M, Setsu N, Yuki K, Ito T, Iwamoto Y, Furue M, Oda Y. Alteration of PDGFRβ-Akt-mTOR pathway signaling in fibrosarcomatous transformation of dermatofibrosarcoma protuberans. Hum Pathol. 2017; pii: S0046-8177(17)30241-1. [Epub ahead of print]

12. Harati K, Lange K, Goertz O, Lahmer A, Kapalschinski N, Stricker I, Lehnhardt M, Daigeler A. A single-institutional review of 68 patients with dermatofibrosarcoma protuberans: wide re-excision after inadequate previous surgery results in a high rate of local control. World J Surg Oncol. 2017; 15(1):5. https://doi.org/10.1186/s12957-016-1075-2 PMid:28056985 PMCid:PMC5217543

13. Farma JM, Ammori JB, Zager JS, Marzban SS, Bui MM, Bichakjian CK, Johnson TM, Lowe L, Sabel MS, Wong SL, Douglas Letson G, Messina JL, Cimmino VM, Sondak VK. Dermatofibrosarcoma protuberans: how wide should we resect? Ann Surg Oncol. 2010; 17(8):2112-2118.

14. DuBay D, Cimmino V, Lowe L, Johnson TM, Sondak VK. Low recurrence rate after surgery for dermatofibrosarcoma protuberans: a multidisciplinary approach from a single institution. Cancer. 2004; 100(5):1008-1016. https://doi.org/10.1002/cncr.20051 PMid:14983497

15. Veronese F, Boggio P, Tiberio R, Gattoni M, Fava P, Caliendo V, Colombo E, Savoia P. Wide local excision vs. Mohs Tübingen technique in the treatment of dermatofibrosarcoma protuberans: a two-centre retrospective study and literature review. J Eur Acad Dermatol Venereol. 2017; 31(12):2069-2076. https://doi.org/10.1111/jdv.14378

16. Paradisi A, Abeni D, Rusciani A, Cigna E, Wolter M, Scuderi N, Rusciani L, Kaufmann R, Podda M. Dermatofibrosarcoma protuberans: wide local excision vs. Mohs micrographic surgery. Cancer Treat Rev. 2008; 34(8):728-36. https://doi.org/10.1016/j.ctrv.2008.06.002 PMid:18684568

17. Rutkowski P, Van Glabbeke M, Rankin CJ, Ruka W, Rubin BP, Debiec-Rychter M, Lazar A, Gelderblom H, Sciot R, Lopez-Terrada D, Hohenberger P, van Oosterom AT, Schuetze SM; European Organisation for Research and Treatment of Cancer Soft Tissue/Bone Sarcoma Group; Southwest Oncology Group. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol. 2010; 28(10):1772-1779. https://doi.org/10.1200/JCO.2009.25.7899 PMid:20194851 PMCid:PMC3040044

18. Rutkowski P, Klimczak A, Ługowska I, Jagielska B, Wągrodzki M, Dębiec-Rychter M, Pieńkowska-Grela B, Świtaj T. Long-term results of treatment of advanced dermatofibrosarcoma protuberans (DFSP) with imatinib mesylate - the impact of fibrosarcomatous transformation. Eur J Surg Oncol. 2017 ; 43(6):1134-1141. https://doi.org/10.1016/j.ejso.2017.03.011 PMid:28365129

19. Wang C, Luo Z, Chen J, Zheng B, Zhang R, Chen Y, Shi Y. Target therapy of unresectable or metastatic dermatofibrosarcoma protuberans with imatinib mesylate: an analysis on 22 Chinese patients. Medicine (Baltimore). 2015; 94(17):e773. https://doi.org/10.1097/MD.0000000000000773 PMid:25929918 PMCid:PMC4603059

20. Ugurel S, Mentzel T, Utikal J, Helmbold P, Mohr P, Pföhler C, Schiller M, Hauschild A, Hein R, Kämpgen E, Kellner I, Leverkus M, Becker JC, Ströbel P, Schadendorf D. Neoadjuvant imatinib in advanced primary or locally recurrent dermatofibrosarcoma protuberans: a multicenter phase II DeCOG trial with long-term follow-up. Clin Cancer Res. 2014; 20(2):499-510. https://doi.org/10.1158/1078-0432.CCR-13-1411 PMid:24173542

21. Miyagawa T, Kadono T, Kimura T, Saigusa R, Yoshizaki A, Miyagaki T, Yamada D, Masui Y, Fujita H, Sato S. Pazopanib induced a partial response in a patient with metastatic fibrosarcomatous dermatofibrosarcoma protuberans without genetic translocations resistant to mesna, doxorubicin, ifosfamide and dacarbazine chemotherapy and gemcitabine-docetaxel chemotherapy. J Dermatol. 2017; 44(3):e21-e22. https://doi.org/10.1111/1346-8138.13717 PMid:27988943

22. Mir O, Brodowicz T, Italiano A, Wallet J, Blay JY, Bertucci F, Chevreau C, Piperno-Neumann S, Bompas E, Salas S, Perrin C, Delcambre C, Liegl-Atzwanger B, Toulmonde M, Dumont S, Ray-Coquard I, Clisant S, Taieb S, Guillemet C, Rios M, Collard O, Bozec L, Cupissol D, Saada-Bouzid E, Lemaignan C, Eisterer W, Isambert N, Chaigneau L, Cesne AL, Penel N. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016; 17(12):1732-1742. https://doi.org/10.1016/S1470-2045(16)30507-1