# Dermatofibrosarkoma protuberans: clinics, diagnostics and treatment

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**Summary**. Dermatofibrosarkoma protuberans (DFSP) is characterized by a high frequency of recurrence and a low risk of metastasis. The mass fraction DFSP is 1% of soft tissue sarcomas. The disease is most common in patients 20–50 years old and mainly localized on the trunk, especially on the chest wall and the shoulder girdle; on the genetic level the cause of DFSP is the mutual translocation of t(17;22)(q22; q13). The unfavorable prognostic factors for DFSP is the advanced age of patients, the tumor size more than 5 cm, the location on the area of head and neck, the high mitotic index, p53 mutation and the increased number of cells in the histological preperation. The most effective method of surgery treatment is microscopically controlled operation for Mohs, which leads to the smallest number of relapses. As an adjuvant treatment of positive edges of the resection can be used radiotherapy by the total focal dose 50–60 Gy. With the local widespread and the metastatic DFSP is using the inhibitor of the tyrosine kinase imatinib.

**Key words**: dermatofibrosarkoma, genetics, diagnosis, imatinib, surgical treatment.

Dermatofibrosarkoma protuberans – a very rare tumor, which is characterized by locally aggressive growth and a high rate of recurrence and at the same time, the low risk of metastasis. In 1980 Sherwell S. [31] and Taylor R.W. [35] independently described this nosology as progressive and attributable to develop recurrences after the surgical abscission. The term “dermatofibrosarkoma protuberans”, which refers to the tendency of the tumors to form the nodes protruding above the skin, was proposed in 1925 by Hoffman E. [13].

Mass fraction of the DFSP is 0,01% of all the malignant tumors and 1% of the soft tissues sarcomas [5,10]. The disease can develop at any age, but the most common is between 20 and 50 years. According to the literature from 6% to 20% of the patients with DFSP are children. Due to the experts a large proportion of the DFSP appears in childhood, but is diagnosed in adults over asymptomatic and slow growth.

Although DFSP occurs among all races, the sickness rate for the black population is in 2 times higher than in other populations, as confirmed by a recent analysis of 2885 cases [6].

Analysis of the distribution by sex showes the same frequency of lesion among men and women.

DFSP is mainly localized on the trunk, especially on the chest wall and shoulder-girdle (40-50%). Rarely a tumor develops in the proximal parts of the extremities (30-40%), while more often upper extremities are affected. In 10-15%, the tumor is localized on the head (scalp, cheeks) and neck (supraclavicular area) [10, 30].

Possible causes of the appearance DFSP are different skin traumas, particularly by chemical or thermal burns [27], after radiotherapy as well [21]. In support of this theory, emergence of the primary tumor in postoperative scars [20] and scars after the vaccination [21]. Having a history of trauma occurs in 10-20% of cases.

At the genetic level, the cause of DFSV is mutual translocation t(17; 22)(q22;q13) [25,26]. These chromosomal rearrangements lead to the fusion of the gene platelet-derived growth factor B (TFRV) on chromosome 22q13.1 and the gene of the alpha chain type 1 collagen in 17q21 [33]. The main result of translocation t(17;22)(q22;q13) is TFRV overproduction by tumor cells, leading to receptor activation TFRV, which both are type III receptor tyrosine kinase. Detection of these autocrine and paracrine activation mechanisms has led to the assumption that the inhibitors of tyrosine kinases, including imatinib, can be used to treat patients with DFSP as neoadjuvant therapy to reduce tumor size for local spreading disease or with the presence of metastases.

The main feature of DFSP is locally destructive growth and high rate of recurrences after surgical treatment.

The clinical course is divided into two phases. The first phase (plaque) declares itself by a flat painless lesion brown or purple in color , firm texture, which infiltrates the skin, but doesn’t destroy underlying structures. The first phase is characterized by the expansion of plaque on the periphery and can last for years or even decades.

For the second phase (tumor) is inherent the formation on the plaques surface multiple painless nodes of the thickening skin with intense bluish or brownish-red tint. Sizes of the nodes can vary from 2 to 5 cm, and in severe cases

can reach up to 20 cm and have multiple satellites. With the progression of the disease ulceration , hemorrhage , pain of tumor sites can be observed . Usually DFSP is localized in the borders of the skin and doesn't affect deeper tissues , but often untreated or recurrent tumors can spread to fascia, muscles and even bones.

Mostly diagnostic errors occur at the earliest stages of the disease . Differential diagnosis is to be make with diseases such as keloid scar, nodular melanoma, epidermal cyst, dermatofibroma , neurofibroma and scleroderma .

If you suspect DFSP, the incisional or trepan – biopsy is to be done. The diagnosis must be confirmed by histological and/or immunohistochemistry studies. Before the surgery MRI is conducted to assess the depth of tumor`s penetration into underlying tissues. CT is used only in cases of suspected lesions of the skeletal system.

Histologically DFSP consists of densely deployed spindle cells with elongated nucleis and a small amount of cytoplasm, infiltrates the dermis and is distributed to the subcutaneous tissue. Between the cells connective tissue fibers are situated, mainly precollagen and retikulin. Mature collagen fibers are found on the periphery of the tumor, where as well are focuses of fibrosis . Fibroblasts and fibers form a structure in the form of "turbulence", fascicles going in different directions, sometimes in the form of rings. This location provides histologically similarity to "Moire". The degree of differentiation of tumor cells in different parts of the tumor are not the same. However, cells with large atypical nuclei and abnormal mitoses are rare. Giant cells are few or absent. In tumor stroma in places are defined areas mucilagination. The tumor usually occupies the entire dermis and penetrates the subcutaneous fat. A typical diagnostic feature of DFSP is appearence along with a great node the smaller satellites. The epidermis is atrophic, sometimes with signs of invasion of the tumor cells and destruction [2].

There are several histological subtypes of DFSP : pigment ( Bednar`s tumor ) [4,8], giant fibroblastoma [32], atrophic [18], sclerogenous [7,12,29], granulated , fibrosarkomatosed , miksoyid and mioyid . All above mentioned subspecies of DFSP have some differences in the microscopic structure (Table 1).

Table 1. Histological subtypes of DFSP

| Hystological subtype of DFSP | Characteristics of the histological structure. | Expression of IHC markers |
|---|---|---|
| Pigment (Bednar`s tumor) | Occurrence of the spindle like cells mixed with the 3 nonhomogenous population of the melanin-holded dendrite cells. | CD34+ S100- |

| | | |
|---|---|---|
| Giant-cell fibroblastoma | Affection of the derma and subcutaneous fat. It consists of the ovoid fibroblasts, multinuclear giant cells with polisegmental nucleus and pseudo vascularized spaces. Pseudo sinusoids are not covered inside with the endotelian cells and penetrates in the form of tentacles to the subcutaneous fat. | CD34+ S100- |
| Atrophic | Reduction of the thickness of the derma to 50% в compare to the surrounding one. The big amount of the spindle like cells. | CD34+ S100- |
| Sclerogenous | Occurrence of more than 50 % collagen fibers, between those typical histological focuses DFSP are located. | CD34+ S100- |
| Granular-cell | Mixure of the spindle like cells та cells with multiple lysosome granules, round excentric nucleus and prominent endosomes. | NK1C3+ S100- |
| Fibrosarcomatous | Hypercellularity, multiplicity of the atypical cells, augmentation of the number of mitosis, invasion to the subcutaneous fat, vessels та muscels. | CD34- p53+ |
| Mixoid | Occurence of the stellate or spindle like cells with multiple accumulation of the hyaloronidase sensitive mucin в intercellular space. | CD34- S100- |
| Myoid | Occurence of the myoid areas dispersed by the whole tumor, which don`t have a connection with capillary follicles or with the walls of the vessels. | CD34- Desmin- Smooth muscle actin+ |

The main immunohistochemical markers for DFSP is CD34, which is expressed in 80-100 % of cases. At the same time, 10-20% of DFSP this marker is negative, usually in for the fibrosarkomatosed tumor that is the most aggressive. It should be noted that the expression of CD34 can occur in other forms of sarkoms [9,34], particularly in miofibrosarkomas , epithelioid sarcomas, angiosarcomas , and even in some benign fibrohystiocityc lesions (fibroma, fibromiksoma , dermatofibroma). For differential diagnosis between DFSP and fibrous histiocytoma a marker XIIIa is used, which in 85-90 % of cases is negative for DFSP.

In recent years there have been studies on specific immunohistochemical markers: CD 163, stromelysinIII [3,14], nestyn [23], but today they are not used for routine practice.

Unfavorable prognostic factors for DFSP are elderly age of patients, tumor`s size more than 5 cm, location in the area of head and neck, high mitotic index, p53 mutation and increased amount of cells during histological examination.

The main treatment of DFSP is surgery. However, the question of the minimum margin from the edge of the tumor to achieve the local control remains uncertain. High level of DFSP recurrence after the surgical removal may be explained by an eccentric tumor growth, in which individual cells penetrate into the subcutaneous tissue. Formation of the tentacle like clusters of cells lead to the appearing of tumor sites away from the primary focus. These clusters for the time are not detected clinically and may be omitted if the detection of the purity of the edges resection is not carried.

According to the literature the recurrence rate of DFSP after economical excision (space from the edge of the tumor is less than 1 cm) ranged from 20 to 60% [15,24]. After wide excision (2-3 cm) local recurrences occur much less frequently - from 0 to 30% [15,24], and at 5 cm ,margin incidence of the recurrence is less than 5% [15,1] (Table 2). Thus, increasing the limit of indention from the edge of the tumor significantly reduces the incidence of local recurrence.

Table 2. The incidence of local recurrences, depending on the type of surgery

| Author | Year | Economic excision (less than 2 sm) | Wide excision (2-3 sm) | Micrographic surgery by Mohs |
|---|---|---|---|---|
| Dubai D. | 1984 | - | 0 % | 0 % |
| Rutgers E.G. | 1992 | 50 % | 13 % | - |
| Gloster H.M. | 1996 | 43 % | 18 % | 0,6 % |
| Bowne W.B. | 2000 | 85 % | 15 % | - |
| Paradisi A. | 2008 | - | 13,2 % | 0 % |
| Love W.E. | 2009 | - | 11 % | 0 % |
| Llombart B. | 2011 | - | 17 % | 0 % |

DFSP metastasizes only in 2-5 % of cases, mainly in the lungs, because all patients must perform radiography of the chest cavity, and for suspected metastatic lesions — computed tomography.

Performing a wide indention from the edge of the tumor is not always possible , especially when the tumor in the face and neck , as well as for the children. Expanding the boundaries of surgery leads to the necessity to perform more complex plastic surgery, which increases the level of postoperative complications and may leave serious cosmetic defect .

Currently, the golden standard of surgical treatment of DFSP is microscopically controlled surgery by Mohs, after which recurrences occur less than in 1% cases (0 to 8.3%) [17]. Microscopically controlled surgery by Mohs permits to determine tentaclelike clumps of DFSP cells and to remove residual tumor.

Methodology for this operation consists of several stages. At the beginning is performed DFSP removal with indention from the visible tumor boundaries from 0.5 to 1 cm ,and the knife is held at an angle of 45. Skin defect is temporarily closed by bandage before it is proven the complete tumor removal. The labeling of removed tissue and the wound edges are performing and photographing. Removed preparation is divided into separate sections, with precise indication of their anatomical orientation , and then the sections are fixed in formalin and filled with paraffin. To investigate DFSP frozen sections are not used because it complicates the determination of the infestation in the subcutaneous tissue. Unlike wide excision , while vertical sections of paraffin blocks are made, for Mohs surgery are used only horizontal serial sections. Sections are stained with hematoxylin and eosin (H & E); diagnosis is confirmed by immunohistochemical study of CD34. In patients with positive resection margins conduct re-excision of residual tumor with indention 0.5 cm. The process is repeated until the absence of microscopic tumor. After reaching negative edges resection (R0) the stage reconstruction of tissues is produced. Skin wound closure of plastic defect can be performed using local tissues, free skin flap or a combination of these methods.

In cases when surgical removal of the tumor is not possible ( in locally-spreaded and metastatic DFSP ) alternative to surgery are targeted therapy and radiation treatment .

As a targeted therapy tyrosine kinase inhibitor imatinib is used , which was first used as a palliative therapy for 4 patients with metastatic DFSP . In 2 cases the effect was temporary: pulmonary metastases decreased in size and number , but not completely disappeared. For the other 2 patients the complete regression of the tumor was achieved. These encouraging results led to a new research and today imatinib is included in the standards of treatment of locally - spreaded and metastatic DFSP in most European countries and the United States (Table 3) [19].

It should be noted that in the absence of translocation t ( 17; 22 ) (q22; q13) tyrosine kinase inhibitor therapy is ineffective , it is desirable to perform molecular analysis of tumors by polymerase chain reaction or fluorescence in situ hybridization before use of imatinib.

Table 3. Effectiveness of the use of imatinib in the DFSP treatment

| Trial | Year | The number of patients | Objective reponse |
|---|---|---|---|
| Maki R.G. | 2002 | 4 | 2 CR, 2 SD |
| McArthur G. | 2005 | 10 | 4 CR, 5 PR, 1 SD |
| Heinrich M. | 2008 | 12 | 4 CR, 6 PR, 2 PD |
| Kerob D. | 2010 | 25 | 9 CR, 16 PR |
| Llombart B. | 2013 | 100 | 50 CR |

* CR - complete response (CR), PR - partial response (partial regression), SD - stable disease (disease stabilization), PD - progressive disease (progression of disease)

Histologically investigation of deleted DFSP after imatinib treatment in some cases detects little celled fibrovaskulised or even scar tissue , while others - intact tumor. Some scientists believe that imatinib induces apoptosis of tumor cells and its complete destruction, while others hold to the idea that under the influence of treatment DFSP changes its phenotype , which as a result reduces proliferation and tumor size.

In the literature there are isolated reports of the use of chemotherapy-doxorubicin and ifosfamide in metastatic DFSV.

Despite the fact that DFSV is radiosensitive tumor, the role of radiation therapy remains to be fully defined. In 1996 Ballo M.T. reported on the use of radiation therapy at a dose of 50-60 Gr. in the adjuvant setting mode for 19 patients with DFSP, 6 of whom had positive microscopic resection edges. After 10 years of supervision the recurrence was detected only in one patient. In 2000, Sun M.L. published the data on the treatment of 35 patients with DFSP, 11 of whom received adjuvant radiotherapy. Recurrences of the tumor were detected in 9 ( 37.5%) patients who performed a surgery, and 2 (18.2%) patients, who received a combination therapy.

Generally considered today is the use of the radiotherapy at the positive edges of resection after surgery when reexcition is impossible, as well as for large tumors, even in the occurrence of negative edges resection.

Patients after radical treatment for DFSP must be under the supervision and undergo the checkups every 6 months for the first 3 years of observation, when the greatest risk of recurrence is. After the 3d year, checkup must be performed annually. The greatest attention should be paid to inspection and palpation of the postoperative scarrings.

***Clinical case***. *Patient A. , 1960 visited the oncoorthopedic, tumors of the skin and soft tissues department of the National Cancer Institute of Ukraine in August 2013 with complaints of the presence of the recurrence of tumor in the postoperative scar area in the projection of the left scapula and multiple tumors of the soft tissues of the back and chest.*

*History of the disease. In 1995 she noticed the appearance of the tumor in the projection of the left scapula , which gradually increased in size and began to ache during the palpation , the skin over the tumor became bluish in color . In 1997 patient went to the hospital . After the examination, the excision of the tumor was performed with margin from the edge less than 1 cm. Histological conclusion: dermatofibrosarkoma . In 2000 patient visited our Clinic with the recurrence of the tumor in the area of post-surgical scar. 08.04.2000 was performed the excision of the recurrence with margin from the edge of the tumor up to 2 cm. Diagnosis of dermatofibrosarcoma was confirmed histologically. At the beginning of 2013 she noticed a recurrence of the tumor in the area of postoperative scar and soft tissue tumors in the area of right scapula . 19.04.2013 was performed a wide excision of tumor recurrence and tumor of soft tissue in the area of right scapula with a margin from the visible edge of the tumor to 3 cm. Histopathological conclusions : Exploding Dermatofibrosarkoma protuberans, low degree of differentiation (G3).*

*In August 2013 the patient went to the hospital with the recurrence of the tumor in the area of postoperative scar and multiple tumors of the soft tissues of the back, chest.*

*After further examination the first course of chemotherapy was conducted scheme: ifosfamide 5000 mg/m2 on days 1-2 intavenous , doxorubicin 50 mg/m2 on day 1 intravenous (IA) . After the 3 week, during the checkup , the progression of the desiase was identified, which manifested appearenced of the tumors in the subcutaneous fat of the right shoulder, anterior chest wall, abdominal wall area on*

*the right. Replacement of the chemotherapy was performed : ifosfamid 5000 mg/m2 on day 1-2 intravenous, doxorubicin 50 mg/m2 on day 1 intravenous, dakarbazini 800 mg/m2 on day 1 (MAID).*

*At present the patient continues treatment.*

## Conclusion

1. DFSP is a rare tumor that affects the dermis and may extend to underlying tissue.
2. DFSV prone to local recurrence.
3. The most effective treatment is microscopically controlled surgery by Mohs, which leads to the smallest number of recurrences.
4. As an adjuvant treatment for positive resection edges can be used radiotherapy 50-60 Gr.
5. When locally spreading and metastatic DFSP relatively effective systemic therapy is a use of tyrosine kinase inhibitor.

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