Review Article

Dermatofibrosarcoma Protuberans: A Systematic Review of The Literature

Abstract:

Background: Dermatofibrosarcoma Protuberans (DFSP) is a rare slow growing cutaneous soft tissue sarcoma, that is characterized to be locally invasive with high recurrence rate. However, it has poor metastatic capacity.

Objective: We are conducting this literature review to gather evidence-based medicine knowledge regarding Dermatofibrosarcoma Protuberans. Moreover, this study highlights the gaps of knowledge in regard to this disease entity.

Methods: The literature search was conducted by searching the keywords "Dermatofibrosarcoma Protuberans" and "soft tissue sarcomas" in PubMed and Web of Science databases.

Results: 1,769 potentially relevant results showed matched titles, of which 13 articles met the requirements and were included in the literature review.

Limitations: Vague nonspecific clinical manifestations, makes it challenging to establish an early diagnosis and seek an appropriate counseling. In addition, it is difficult to diagnose due to the slow growing behavior and the tumor's benign appearance. As a result of all of that there is no enough cases reported in the literature.

Conclusion: This review highlights the need of high index of suspicion to help reach an early and proper diagnosis and to raise awareness. Dermatofibrosarcoma Protuberans needs a

specialized center in order to identify and recognize the disease. The knowledge and awareness of the disease is low since it is rare.

Keywords: Dermatofibrosarcoma Protuberans, soft tissue sarcoma, skin cancer, superficial skin lesions, dermato-surgery.

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Search Strategy:

A systematic review was done of the included articles for this current study from September 13, 2020 to September 22, 2020 using the keywords: “Dermatofibrosarcoma Protuberans” and “soft tissue sarcoma”. The data were obtained from a thorough search from two main electronic databases: PubMed and Web of Science yielding 1,769 matched results, where 13 articles were chosen. The disease entity of Dermatofibrosarcoma Protuberans was covered thoroughly with a focus of its histopathological findings and new treatment modalities.

Introduction:

Dermatofibrosarcoma Protuberans (DFSP) Is a low to intermediate rare superficial soft tissue sarcoma. It is a cutaneous cancer that is derived from the dermis, the middle layer of the skin. DFSP was first described back in 1980 by Taylor. Followed by establishing DFSP as a distinct histopathological entity by Darier and Ferrand in 1924. In 1925, it was named by Hoffman [1]. In fact, it is a type of sarcoma that is known to have low metastatic potential. However, it is characterized to be locally invasive. Since this cancer can invade the deep layers including: sub-

cutanous tissue, muscles, and even bones; it is documented to have high recurrence rate. The prevalence is more in black ethnic group with a male to female ratio of 1 to1, affecting the younger age groups between the age of 20 to 59 years of age. This tumor most commonly affects the trunk and proximal upper extremities, but it is also reported to arise in other anatomical distribution. It classically occurs in the covered areas not exposed to the sun, in contrast to most of the other types of skin cancers that affects the sun exposed areas. There is no linked disposing factors that are proven until now to cause DFSP. There is no significant symptoms the patient can suffer from, the disease takes an indolent course, thus leading the disease going unnoticed. In order to make a diagnosis, a tissue biopsy or an excision is resected and sent to a dermato-pathologist using an immunohistochemical tests. Surgical resection by MMS surgery is the mainstay treatment option. Other treatment modalities such as radiotherapy, chemotherapy and tyrosin kinase inhibitors should be considered in cases where we are not able to reach a negative margin or where recurrence of the tumor occur. [2]

Epidemiology:

DFSP is documented to be more common in black ethnicity, a male to female ratio of 1 to 1, however, some studies suggested a slight male predominance. It classically develops in the 20 to 59 decades of life, with less common incidence affecting pediatric or geriatric age groups. 0.8 to 5 patients per million population are diagnosed each year with DFSP. The disease represents 1% of all superficial soft tissue sarcomas [3].

The lesion arises from the second layer of the skin called the dermis. It develops in the non-sun exposed areas where the trunk is the most common site by (42% to 60%) of cases, second location is proximal extremities with the upper limbs accounting for (23% to 25%), followed by lower extremities by (18 %), and finally the head and neck region by (10 to 16%). Having said that, infrequite anatomical distribution have been reported, such as the breasts and genital areas including the vulva and penis] 3[.

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Clinical manifestations and risk factors:

There are not proven risk factors known until now to cause this soft tissue sarcoma. But it is hypothesized that there is a genetic correlation involved. No family history association have been documented. Certain case reports reported prior chronic injury to the areas where the tumor arises, such as prior trauma, old scar, or immunization in the site of the development of DFSP. Regardless of that, DFSP frequently arises on healthy skin in a larger scale of cases.

There are no specific symptoms, however, the lesion gross description is as follows:

DFSP is characterized as a painless lesion that starts small in size, flat in shape, pink or violent in color. In addition, the lesion is asymmetric with ill-defined margins, and finger like projections. lesion. The tumor proliferates slowly over a course of years. As the lesion grows, it has a potential to ulcerate, bleed, and become necrotized. Moreover, it is locally invasive, with a potential to invade up to 0.3-12 cm peripherally and vertically deep into the internal structures reaching the viscera and bones [3]. It is known that the metastasis is rare, but when it occurs, it

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metastasizes into the lymph nodes and the lungs. Recurrence rate is high and common especially if negative margins were not obtained and the tumor was not completely resected laterally and deeply.

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These clinical features justify the difficulty in making a proper diagnosis. Since the lesion is painless, and grows very slowly. Also, it appears like an old scar or a benign cyst, the patient will not complain and will not be concerned. As a result, the diagnosis needs high index of suspicion and a specialized center with multidisciplinary team approach]2[.

Pathophysiology:

The early event happens when a new mutation takes place in a healthy cell and gives rise to four main histopathological variants, which are Myxoid DFSP, Bednar tumors, Giant cell fibroblastoma, and lastly Fibrosarcomatous (FS) DFSP. A translocation of a t(17, 22) gene and a binding of collagen type 1 alpha 1 growth factor genes mainly platelet-derived growth factor subunit b (PDGFB) resulting in activation and stimulation of tyrosin kinase receptors. Once tryrosin kinase receptors are activated, unprogrammed cell proliferation will follow and will lead to the abnormal tumor growth, and from here comes the name “Protuberans” which means lump of tissue. Targeted molecular therapy of tyrosin kinase inhibiters have a role in inhibition of tyrosin kinsise receptors and as a result leading to depressive effect on the cell proliferation]1[.

Histology:

Histologically, DFSP evaluation is challenging given histologic similarities to other fibroblastic soft tissue tumors. DFSP microscopic examination will show a spindle cell proliferation in an irregularly whorled or storiform pattern oriented parallel to the skin surface, often surrounding subcutaneous fat to form a honeycomb appearance. Involvement of the fascia, underlying muscles, periosteum and bone is a late event]2[.

One of the predominant features of DFSP is the ability to penetrate surrounding tissue, with tumor cells invading subcutaneous tissue in the form of irregular finger-like projections through the septa and fat lobules]4[. These tumor extensions contain few cells, and at first glance, it can appear identical to normal fibrous tracts. This makes it hard to determine the exact extent of the tumor and perhaps why recurrences appear after excision with wide margins.]4[.

The presence of a sarcomatous changes in DFSP is a sign of tumor progression, it increases the tumor grade from low to intermediate, but the effect on prognosis is still debated. Mostly, sarcomatous component suggest worse prognosis and a higher rate of metastases.

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Immunohistochemical profile:

The main diagnosis of DFSP is usually based on the immunohistochemical and routine histopathological features. Despite this classic pattern, DFSP can be challenging to differentiate from other tumors on hematoxylin and eosin staining and might require immunohistochemical staining]3[. A typical staining profile for DFSP includes expression of CD34 which is considered characteristic for the diagnosis of DFSP. CD34 often positive in DFSP (80%-100% of DFSP express this marker) and negative for factor XIIIa (2013). CD34 is one of the most effective stains to differentiate DFSP from other soft tissue tumors.

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The sensitivity of CD34 Immunohistochemistry in DFSP ranges from 84 to 100 percent, whereas between 2.5 and 5 percent of dermatofibromas stain positively. Hence, the reliability of CD34 staining is not accurate]4[.

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Moreover, a new study suggests utility for Immunohistochemistry staining for CD44 and hyaluronate in the differential diagnosis of DFSP and dermatofibroma. DFSP tends to be strongly positive for hyaluronate, whereas CD44 is significantly reduced or absent. In contrast, The cells of dermatofibromas tend to stain intensely for CD44, when its stroma stains slightly for hyaluronate]4[.

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Biological sub-types:

There are numerous histologic variants of DFSP including giant cell fibroblastoma (GCF), pigmented, myxoid, atrophic, and DFSP with fibrosarcomatous change (DFSP-FS)]3[. The primary myxoid variant is characterized as containing more than 50% myxoid stroma. Histologically, myxoid DFSP shows the classic infiltrative growth pattern, honeycomb appearance along with CD34 positivity present in DFSP. Myxoid DFSP is differentiated by sheetlike, bland spindle cells along with pale stroma and lobular proliferation]3[.

The Bednar tumor (pigmented variant) accounts for less than 1% of DFSPs. It is found most commonly in the pediatric population and African Americans. As with classic DFSP, it presents most commonly on the extremities and extremities.
Moreover, Bednar tumors are identical to the classic DFSP, except for the presence of melanin. Furthermore, the Bednar tumor is less aggressive with lower rates of local recurrence. It is crucial to differentiate Bednar tumors from other pigmented lesions such as melanoma, because the management and the outcomes are different.]3[

Atrophic or morphea-like DFSP, a rare form of DFSP has been documented. Atrophic DFSP appear like other benign lesions such as idiopathic atrophoderma, morphea, , atrophic scar, anetoderma or lipoatrophy. Mostly, it affects young to middle aged adults. If not fully excised, a high rate of local recurrence will occur. Metastases are rare and generally occur after recurrent local recurrence]5[.

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DDX:

The clinical differential diagnosis of dermatofibrosarcoma protuberans (DFSP) is broad, and can include a number of diseases, depending on the location and size of the tumor. The nodular form of DFSP may be clinically confused with neurofibroma, leiomyoma, epidermal (sebaceous) cyst, malignant melanoma, basal cell carcinoma, keloid, desmoid tumor, dermatofibroma, lipoma, nodular fasciitis, sarcoidosis, and other cutaneous soft tissue sarcomas including Kaposi sarcoma, fibrosarcoma/fibromyxosarcoma, liposarcoma, leiomyosarcoma, angiosarcoma, and undifferentiated/unclassified soft tissue sarcoma.]4[

Management and treatment:

Dermatofibrosarcoma protuberans presents as an asymptomatic, skin-colored to red-brown indurated plaque which may develops to multiple raised violaceus to red-brown nodule. The atrophic variant presents as a violaceous plaque , the tumor sometime ulcerate and become painful.

The majority of DFSPs occur on the trunk , followed by the extremities and then head and neck The shoulder and pelvic region are characteristic area , The tumor known to have growth with asymmetric, root-like projections which cannot be appreciated on clinical exam. Thus, local recurrence following excision is common. Distant metastasis is rare,The lung is the most common site of metastasis]6[.

The treatment of DFSP often requires a multidisciplinary approach. Depending on location, dermatologic surgeons, surgical oncologists, head and neck surgeons, neurosurgeons, plastic surgeons, medical oncologists

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Mohs micrographic surgery (MMS) is the preferred method when available , most of the DFSP cases are often advanced cases; thus, dermatologic surgeons obtain clear margins peripherally and other surgical specialties assist with resection of the fascia and any critical deeper structures. When MMS is not available, wide local excision (at least 2- to 3-cm margins of resection) with pathologic assessment of margin status is recommended] 1. [

WLE was the most common surgical modality used to treat DFSP across the UK local recurrence rate was very low, occurring only after WLE] 7[.

for the treatment of DFSP that is unresectable, recurrent, or metastatic give

. Imatinib mesylate, is a tyrosine kinase inhibitor approved by the US Food and Drug Adminstration in 2006 , Imatinib inhibits the kinase activity of platelet-derived growth-factor receptorβandis taken as 400 mg by mouth once or twice daily. It works for DFSP with t(17;22)with a 50% response rate. In some cases of unresectable DFSP or DFSP that would require mutilating surgery, treatment with imatinib has helped reduce the tumor burden to allow for resection and complete remission .Imatinib does not eradicate metastatic DFSP and there is a strong likelihood that metastatic] 8.[

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They have shown that radiotherapy may improve local control and reduce the risk of recurrence postoperatively in patients with DFSP] 9.[

Prognosis:

The overall prognosis of dermatofibrosarcoma protuberans is good, with a 10-year survival rate of 99.1%. As metastasis is rare, morbidity due to local recurrence is a more common issue. Age older than 50 is a risk factor for local recurrence. Patients with metastatic disease live on average about 2 years after the time of diagnosis. A high mitotic index, increased cellularity, black race, male sex, and location on the head, neck, or limb are risk factors for higher mortality rates]6.[

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Discussion:

Dermatofibrosarcoma Protuberans (DFSP) Is a rare soft tissue sarcoma, is derived from the dermis and have low metastatic potential]6.[However it is locally invasive ,There is no linked disposing factors that are proven until now to cause DFSP, But it is hypothesized that there is a genetic correlation .There is no significant symptoms and takes an indolent course thus leading the disease going unnotice] 1[. The tumor proliferates slowly over a course of years and painless lesions ,small in size These clinical features justify the difficulty in making a proper diagnosis] 7[.Tissue biopsy is done with using an immunohistochemical tests to make diagnosis, DFSP evaluation is challenging given histologic similarities to other fibroblastic soft tissue tumors. microscopic examination will show a spindle cell proliferation in an irregularly whorled or storiform pattern (1 e). CD34 is one of the most effective stains to differentiate DFSP from other soft tissue tumors, Moreover, a new study suggests utility for

Immunohistochemistry staining for CD44 and hyaluronate in the differential diagnosis of DFSP and dermatofibroma. DFSP tends to be strongly positive for hyaluronate, In contrast, The cells of dermatofibromas tend to stain intensely for CD4]4[. The treatment of DFSP often requires a multidisciplinary approach ,Surgical resection by MMS surgery is the mainstay treatment option thus, dermatologic surgeons obtain clear margins peripherally, another surgical option is wide local excision (at least 2- to 3-cm margins of resection)] 1[, local recurrence rate was very low, occurring only after WLE(3n). I

Other treatment modalities such as radiotherapy, chemotherapy and tyrosin kinase inhibitors (Imatnib mesylate) should be considered in cases where we are not able to reach a negative margin or where recurrence of the tumor occur] 7[. The overall prognosis of dermatofibrosarcoma protuberans is good, with a 10-year survival rate of 99.1%.(1n)]6[.

Conclusion:

Dermatofibrosarcoma protuberans (DFSP) is a rare malignant mesenchymal tumor that originate in the dermis and is characterized by latency in its initial detection. Even though DFSP has a low metastatic potential, there is high chance of local recurrence with repeated excisions. Mostly, it affects proximal extremities and trunk particularly areas not exposed to the sun]2[. DFSP represent 1% of all soft tissue sarcomas]3[. DFSP is a result of unprogrammed cell proliferation in which t(17,22) gene translocation occur which will lead to the tumor growth. DFSP is classically diagnosed by IHC and histopathology]3[.The clinical differential diagnosis of

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DFSP is wide, it can be confused with nodular fasciitis, lipoma, desmoid tumor, basal cell carcinoma, keloid and leiomyoma.

DFSP management requires a multidisciplinary approach with Mohs micrographic surgery being the best since most of DSFP cases are diagnosed in advanced stages. DFSP overall prognosis is good.

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