ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 03, pp.66574-66577, March, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

BEHCET'S DISEASE: A HISTOPATHOLOGICAL PERSPECTIVE

Namrata Sarin and *Priyanka Anand

Department, Pathology Department, Hindurao Hospital and NDMC Medical College, New Delhi, India

ARTICLE INFO

Article History:
Received 02nd December, 2017
Received in revised form
28th January, 2018
Accepted 28th February, 2018
Published online 28th March, 2018

Key words:
Oral ulcers, genital ulcers, Recurrent, vasculitis disorder, Behcet.

ABSTRACT

Behcet's disease is an uncommon systemic vasculitis disorder of idiopathic nature. Almost all aspects of the disease are controversial including its diagnostic criteria, classification and pathogenesis. Patients present with frequent oral aphthous ulcers, genital ulcers, skin lesions and ocular lesions. Usually the inflammation is self limiting but relapsing episodes are hallmark of the disease. It also involves the central nervous system, large vessels and gastrointestinal tract. Histopathological and immunohistochemical examination plays an important role in the diagnostic accuracy of these lesions. New treatment modalities aims to target towards cytokines such as TNF-α, IFN-γ, IL-β, IL-6 and IL-8. Prognosis is unfavourable despite various therapeutic advancements. We herein present a case in a 21 year old male with recurrent oral and genital ulcers.

Citation: Namrata Sarin and Priyanka Anand, 2018. "Behcet's disease: a histopathological perspective", *International Journal of Current Research*, 10, (03), 66574-66577.

INTRODUCTION

It is a rare systemic vasculitis disorder of unknown origin characterized by repetitive attacks of oral aphthous ulcers, genital sores and ocular lesions. The triple symptom complex of oral and genital aphthae and uveitis was first outlined by Behcet in 1937 that explains the disease pattern. (Mohamad *et al*., 2016) Clinical features of acute inflammation are usually of lesser duration with relapse of varied intensities. It affects males more than females in a proportion varying from 1.5-5:1 and is associated with significant morbidity and mortality in males.[2,3,4] There is no specific diagnostic tool or serum biomarker to identify and quantify the severity of Behcet's disease (BD) and prognosis is difficult to make. It usually occurs between the third and fourth decades, infrequently developing before puberty and after fifty years of life. Severe clinical manifestations and mortality is associated with an earlier age onset. As per the literature, the disease appears to be of severe degree representing more severe ocular, neurological and cardiovascular clinical manifestations in males. (Mendes *et al*., 2009; Verity *et al*., 1999; Sfikakis *et al*., 2007) BD is also known as silk road disease as its prevalence worldwide ranges from 0.1/1000 to 1/10,000 with a presence in Asian countries 30°- 40° north of equator from Mediterranean to Japan. (Mendes *et al*., 2009; Verity *et al*., 1999) According to the literature, there is a high incidence of familial association in juvenile patients, (Gul *et al*., 2000) with a hereditary alliance of BD in 1-18%. An interrelation with HLA- B51 (HLA Class 1 antigen) has been noted. (Verity *et al*., 1999; Yazici *et al*., 1977) Involvement of skin occurs in 38- 99% of BD patients. (Mendes *et al*., 2009; Sfikakis *et al*., 2007) Patients usually present with papulopustular (28-96%) and acne- like lesions. (Gul *et al*., 2000; Al-Araji, 2009) Skin lesions unveil a wide range of distribution involving the face, trunk, limbs and buttocks (Mendes *et al.,* 2009) and are characterized by vasculitis and thrombosis. (Sfikakis *et al.,* 2007) Early lesions manifest leukocytoclastic vasculitis or neutrophilic vascular reactions with fibrinoid necrosis while fully developed mature lesions exhibit lymphocytic vasculitis (Al-Araji, 2009) Erythema nodosum lesions occur in 15-78% of patients, mostly involving the lower limbs in females. (Sakane *et al.,* 1999)These lesions do not ulcerate and may have a spontaneous remission with residual pigmentation. Cutaneous ulcers are rare and only 3% of BD patients are affected. These ulcers are recurrent, are similar to aphthous ulcers and usually heal with scarring, in the neck; breast; axillae; inguinal region; legs and interdigital skin of feet. (Alpsoy *et al*., 2003) Cutaneous lesions in BD mostly have a favourable prognosis. We present here a case of Behcets's disease in a 21 year old male with typical cutaneous manifestations which were confirmed on histopathological examination.

Corresponding author: **Priyanka Anand,**
Department, Pathology Department, Hindurao Hospital and NDMC Medical College, New Delhi, India.

Case Presentation

A 21 year old male presented with recurrent oral and genital ulcers since five years with multiple painful lesions over the

lower extremities. On examination ulcer was present over the mucosal aspect of upper lip with scarring over the genitalia. Multiple tender nodules were present over the anterior aspect of leg. Systemic examination including the ophthalmic examination was normal. Routine laboratory investigations were within normal limits.

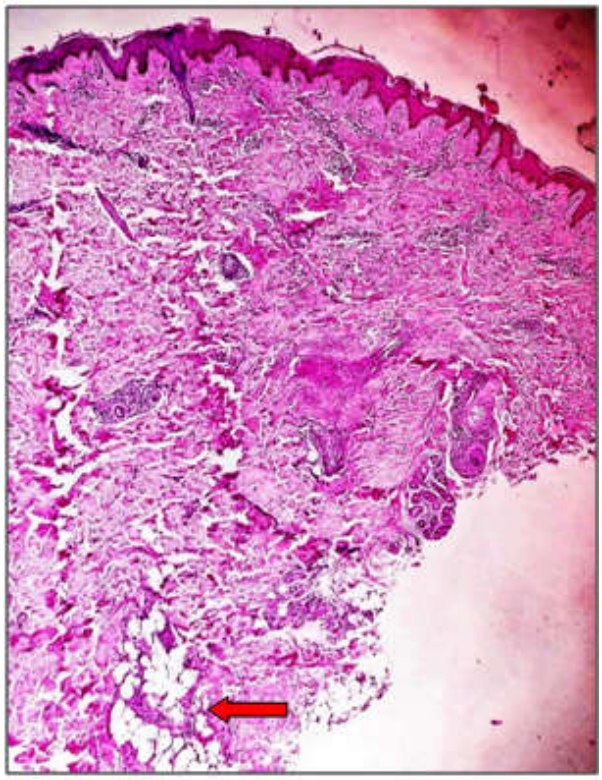

Fig 1. Mictophotograph shows superficial and deep perivascular infiltrate in the dermis as well as subcutaneous fat showing panniculitis (arrow). (4x, H & E stain)

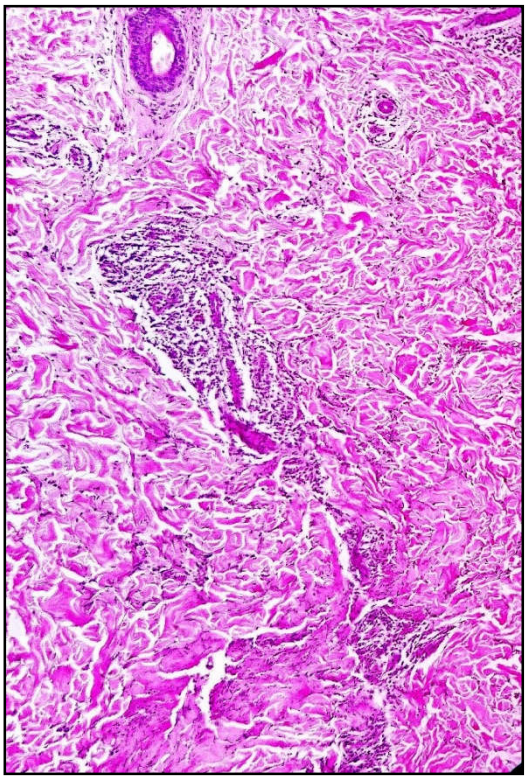

Fig 2. Microphotograph showing vascultis (10x, H & E stain)

Differentials made on clinical grounds were erythema nodosum, erythema induratum and behcet's disease. Biopsy was performed from the lesions over the limb as well as from the pathergy site and sent for histopathological examination. On microscopic examination, overlying epidermis was unremarkable. Dermis showed perivascular mixed inflammatory infiltrate predominantly neutrophils and leukocytoclasis was noted (Fig 2 and 3).

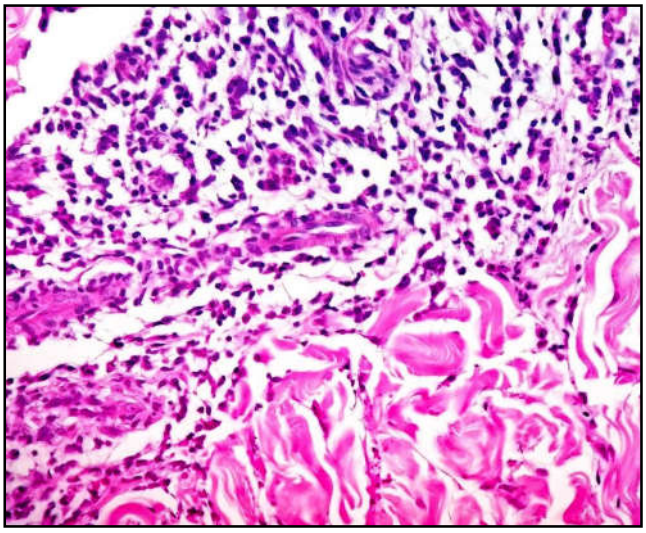

Fig 3- High power view shows mixed inflammatory infiltrate predominantly neutrophils around the vessels with leukocytoclasis. (40x, H & E stain)

Subcutaneous fat showed panniculitis. (Fig 1) Based on these findings along with clinical correlation, a diagnosis of Behcet's disease was rendered. The patient was advised immunosuppressants along with corticosteroids and is currently under follow up period.

DISCUSSION

Diagnosis is confirmed by ruling out other diseases despite the presence of typical triple- symptom complex. (Gul *et al*., 2000) As there is no specific test, diagnosis can be very challenging particularly when symptoms are non- contributory. International Chapel Hill Guidelines were proposed in 1990 and revised in 2012 that stated the presence of recurrent oral ulcerations (atleast three times in one year) accompanied by any two features including recurrent genital ulceration (aphthous ulceration with scarring), eye lesions (anterior uveitis, posterior uveitis, cells in vitreous on slit lamp examination, retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions, acneiform nodules in post- adolescent patients not on corticosteroid therapy) and/ or a positive pathergy test. In this case the patient had recurrent oral and genital ulceration with scarring. He also manifested with tender multinodular skin lesions over the legs. Pathergy is an essential feature of BD which is described by a non- specific skin hyper- reactivity minor trauma.[5] The reading should be noted 48 hours after the procedure and the site of choice is the flexor aspect of forearm. Pathergy lesions are manifested as erythematous papules, at times topped by a sterile pustule. The test is considered positive when a reaction greater than 2mm occurs. Pathergy test was performed in our patient that was positive. Many criterias have been used for the diagnosis, each symbolised by its own clinical features and frequencies.

All criterias necessitated to abide by the three major symptoms initially elucidated by Behcet as a separate clinical entity (oral ulceration, genital ulceration and uveitis). The main international standard for diagnosis was proposed by the international study group for BD. They compared previously defined sets of criteria and originated a completely new set of symptoms. These were last updated in 2013, they excluded subjective and rare features and showed more specificity with little or no loss of sensitivity to methods used before. (de Menthon et al., 2009) Study was conducted by Lawton *et al* in 2004 that defined a set of clinical features to be used as a standard index for measurement of BD activity. (Lawton *et al*., 2004) BD is characterized by episode of relapses and remissions along with periods having few overt clinical symptoms. (Mendes *et al*., 2009) It is estimated that the disease is due to an autoimmune response. The infectious agents or other environmental factors trigger CD4+ T cells activation in genetically susceptible individuals, leading to secretion of cytokines that stimulate inflammation inducing immune cells.

Infectious agents such as bacteria and/ or viruses producing dysfunction in inflammatory response in the patients have been implied in the pathogenesis of the disease. Increased levels of various inflammatory markers including c- reactive protein, erythrocyte sedimentation rate, peripheral leukocyte and platelet count and serum cytokines including TNF-α, IFN-γ, IL-β, IL-6 and IL-8 (Atzeni *et al*., 2005; Link *et al*., 1994) are highly sensitive but not specific to BD. It is considered as a non- ANCA vascultis as auto antibodies such as antinuclear, rheumatoid factor, cryoglobulinemia and antineutrophil cytoplasmic antibodies were not been detected. According to studies, dysbiosis of the gut microbiota and a significant decrease of butyrate production are present in BD patients. As butyrate helps in the differentiation of T regulatory cells, a defect in its production leads to both reduced T reg responses and activation of immune- pathological T- effector responses. (Medzhitov and Janeway, 2002) Other studies have shown predilection to insulin resistance and metabolic syndrome in patients and reduction of angiopoietin-1 especially in those with vascular involvement. (Hatemi *et al*., 2015) According to a Chinese group, high IgG reactivity to an endothelial cell autoantigen had been demonstrated. (Hatemi *et al*., 2016) Correlation between the hyperactive state of neutrophils and BD activity is well understood.

The underlying mechanism is still not known. Antigen presenting cell and T- lymphocyte derived cytokines and chemokines are supposed to play a role in hyperreactivity of neutrophils. (Pay *et al*., 2007) Histopathological examination reveals diffuse necrosis with extensive intraluminal transudative fluid. (Medzhitov and Janeway, 2002) Red blood cells extravasation has also been noted suggesting occlusion with recanalization and focal myonecrosis, are features which are frequently noted along with dense polymorphonuclear infiltration comprising mainly of eosinophils around the arterioles. (Hadfield *et al*., 1997) Around the venules, macrophages are observed and exhibit sparse acute inflammatory infiltrate and mainly lymphocytes. (Oktem-Tanor *et al*., 1999; Desbois *et al*., 2014)Areas surrounding the lesions usually are edematous, show astrocytosis and macrophage infiltrates with scattered microglial nodules. (de Menthon *et al*., 2009) In recent years, there has been an increase in the studies centralised towards histopathological aspects of BD diagnostic mucocutaneous lesions.

There had been an emphasis on the importance of histopathology and direct immunofluorescence in the differential diagnosis. Jorizzo *et al* reported leukocytoclastic vasculitis. (Jorizzo *et al*., 1985) A change in the histopathological features of pathergy in BD patients was studied by Ergun *et al* and they failed to observe a vasculitic pattern. (Ergun *et al*., 1998) There is no difference in direct immunofluorescence on oral aphthae in recurrent aphthous stomatitis (RAS) compared to behcet's disease as shown by Riemer *et al*. (Reimer*et al*., 1983)They found that, compared to non- aphthous oral lesions, oral aphthae of BD and RAS are characterized by C_3 deposition in the vessel wall. IgM deposits were also detected in vessel walls in some patients. Treatment is usually symptomatic due to lack of any etiologic agent. The goals to achieve are towards the functional recovery of visceral involvement and prevention of relapse. Steroids are administered topically or systemically. Relapses are frequently seen after discontinuing steroids. Immunosuppressive drugs have shown to be effective. Due to their delay in action, they are initially given along with corticosteroids as advised in our patient.

Conclusion

BD is a multisystemic relapsing inflammatory disorder with an uncertain etiology and pathogenesis. It is still an ambiguity for clinicians and researchers. Prognosis is unfavourable despite various advancements in the treatment. The main aim is to identify the pathogenesis and target therapy that inhibits the underlying autoimmune inflammatory cascade. New treatment modalities are directed towards targeted cytokines. Histopathological and immunohistochemical evaluation of BD mucocutaneous lesions has become an essential tool to enhance the diagnostic accuracy of these lesions. There have been budding interests for immunofluorescence as it helps in the differential diagnosis of mucocutaneous lesions of BD.

Declarations

Consent for publication: Written informed consent was obtained from the patient for publication of this case report.

Competing interests: None.

Funding: No funding sources.

REFERENCES

Al-Araji, A. 2009. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. *Lancet Neurol*, 8(2):192. doi:10.1016/S1474-4422(09)70015-8.

Alpsoy, E., Donmez, L., Bacanli, A., Apaydin, C. and Butun, B. 2003. Review of the chronology of clinical manifestations in 60 patients with Behçet's *disease. Dermatology*, 207(4):354-356. doi:10.1159/000074113.

Atzeni, F., Sarzi-Puttini, P., Doria, A., Boiardi, L., Pipitone, N. and Salvarani, C. 2005. Behçet's disease and cardiovascular involvement. Lupus. 14(9):723-726. doi:10.1191/0961203305lu2208oa.

de Menthon, M., Lavalley, MP., Maldini, C., Guillevin, L. and Mahr, A. 2009. HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. *Arthritis Rheum*, 61(10):1287-1296. doi:10.1002/art.24642.

Desbois, A., Rautou, P., Biard L, Belmatoug N, Wechsler B, Resche-Rigon, M, *et al*. 2014. Behçet's disease in Budd-Chiari syndrome. *Orphanet J Rare Dis*, 9(1):104. doi:10.1186/s13023-014-0153-1.

Ergun, T. Gürbüz, O. Harvell, J. Jorizzo, J. and White, W. 1998. "The histopathology of pathergy: a chronologic study of skin hyperreactivity in Behcet's disease," *International Journal of Dermatology*, 37(12):929-933.

Gul, A., Inanç, M., Ocal, L., Aral, O., Koniçe, M. 2000. Familial aggregation of Behçet's disease in turkey. *Ann Rheum Dis*, 59(8):622-625. doi:10.1136/ard.59.8.622.

Hadfield, MG., Aydin, A., Lippman, HR. and Sanders, KM. 1997. Neuro-Behçet's disease. *Clin Neuropathol*, 16(2):55-60.

Hatemi, G., Seyahi, E., Fresko, I., Talarico, R. and Hamuryudan, V. 2015. Behçet's syndrome: a critical digest of the 2014¬-2015 literature. *Clin Exp Rheumatol*, 33:S3-14.

Hatemi, G., Seyahi, E., Fresko, I., Talarico, R. and Hamuryudan, V. 2016. One year in review 2016: Behçet's syndrome. *Clin Exp Rheumatol*, 34:10-22.

Jorizzo, J. L. Solomon, A. R. and Cavallo, T. 1985. "Behcet's syndrome. Immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow-up." *Archives of Pathology and Laboratory Medicine*, 109(8):205-214.

Lawton, G., Bhakta, BB., Chamberlain, MA. and Tennant, A. 2004. The Behçet's disease activity index. Rheumatology (Oxford). 43(1):73-78. doi:10.1093/rheumatology/keg453.

Link, J., Söderström, M., Olsson, T., Höjeberg, B., Ljungdahl, A, Link H. Increased transforming growth factor-beta, interleukin-4, and interferon-gamma in multiple sclerosis. *Ann Neurology*, 1994;36(3):379-386. doi:10.1002/ana.410360309.

Medzhitov, R. 2002. Janeway CA. Decoding the patterns of self and non self by the innate immune system. *Science*, 296:298-300. doi: 10.1126/science.1068883.

Mendes, D., Correia, M., Barbedo, M., Vaio, T., Mota, M., Gonçalves, O. and Valente, J. 2009. Behçet's disease—a contemporary review. *J Autoimmun*, 32(3–4):178-188. doi:10.1016/j.jaut.2009.02.011.

Mohamad, J., Zeidan, David Saadoun, Marlene Garrido, David Klatzmann, Adrien Six and Patrice Cacoub. 2016. Behçet's disease physiopathology: a contemporary review. Auto Immun Highlights. 7(1):4. doi:10.1007/s13317-016-0074-1

Oktem-Tanor, O., Baykan-Kurt, B., Gurvit, IH., Akman-Demir, G. and Serdaroglu, P. 1999. Neuropsychological follow-up of 12 patients with neuro-Behçet's disease. *J Neurol*, 246(2):113-119. doi:10.1007/s004150050317.

Pay, S. Şimşek, I. Erdem, H. and Dinç, A. 2007. "Immunopathogenesis of Behçet's disease with special emphasize on the possible role of antigen presenting cells." *Rheumatology International*, 27(5):417-424.

Reimer, G., Luckner, L. and Hornstein, OP. 1983. Direct immunofluorescence in recurrent aphthous ulcers and Behcet's disease. *Dermatologica***,** 167(6):293–298.

Sakane, T., Takeno, M. and Suzuki, N. 1999. Behçet's disease. *N Engl J Med*, 341(17):1284-1291. doi:10.1056/NEJM199910213411707.

Sfikakis, PP., Markomichelakis, N., Alpsoy, E., Assaad-Khalil S., Bodaghi, B., Gul, A, *et al*. 2007. Anti-TNF therapy in the management of behçet's disease-review and basis for recommendations. *Rheumatology (Oxford*), 46(5):736-741. doi:10.1093/rheumatology/kem034.

Verity, DH., Marr, JE., Ohno, S., Wallace, GR. and Stanford, MR. 1999. Behçet's disease, the silk road and HLA-B51: historical and geographical perspectives. *Tissue Antigens*, 54(3):213-220. doi:10.1034/j.1399-0039.1999.540301.x.

Yazici, H., Akokan, G., Yalçin, B. and Müftüoğlu, A. 1977. The high prevalence of HLA-B5 in Behçet's disease. *Clin Exp Immunol*, 30(2):259-261.

****