CASE REPORT

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Behçet's disease with rapidly progressive bilateral optic neuropathy and avascular femoral neck necrosis. Literature review and management update

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Abstract

Behçet's disease is a multi-systemic vasculitis of small arteriolar and venular vessels, which shows a wide range of clinical manifestations, such as oral and genital aphthosis, *erythema nodosum*, panuveitis, complex gastrointestinal disorders, the early onset of neurological involvement being a negative prognostic factor in evolution. We present the case of a 36-year-old patient, who was admitted in the Clinic of Rheumatology for recurrent-neglected oral aphthosis, recurrent *erythema nodosum*, left hip pain, reduction of visual acuity of the right eye, weight loss, profuse sweating, marked fatigability. From the personal history was retained avascular necrosis of right femoral head, with arthroplasty at this level, human leukocyte antigen-B51 (HLA-B51) positive. Ophthalmological evaluation reveals severe bilateral optic neuropathy, with confirmation of neuro-Behçet's disease (NBD) diagnosis, in a Neuro-Ophthalmological Center, based on cerebral nuclear magnetic resonance and cerebrospinal fluid analysis. Associated corticosteroid therapy with Azathioprine was initiated, with no signs of activity and progression of the disease in evolution. The case provides a necessary upgrade of the therapeutic strategies specific to the NBD pattern, emphasizing the importance of the multidisciplinary approach of a patient with complex pathology.

Keywords: neuro-Behçet's disease, optic neuropathy, avascular necrosis, vasculitis.

Introduction

Behçet's disease (BD), vasculitis of small arteriolar and venular vessels, with incomplete elucidated etiopathogenesis, evolution marked by remissions and exacerbations, brings together a wide range of systemic disorders, such as oral and genital aphthosis, *erythema nodosum*, panuveitis, complex gastrointestinal disorders, complex neurological manifestations [1–4].

From the epidemiological point of view, the incidence and prevalence of BD are higher in areas along the old "silk road" – Turkey, Iran Japan –, where the severity of the disease is higher [5–7].

BD is pathologically characterized by neutrophilic infiltrates, nuclear "dust" and erythrocyte extravasation, with or without fibrinoid necrosis, vasculitis can be sometimes leukocytoclastic-like [8–10].

The *International Criteria for Behçet's Disease Classification* revised in 2013 propose a scoring system for skin–mucosal, ocular, neurological, vascular manifestations and positive pathergy test, with a specificity of 89.6% and a sensitivity of 93.9% for BD diagnosis [11, 12].

Eighty percent of patients with BD have ocular manifestations, such as anterior and posterior uveitis, hypopyon with secondary glaucoma, cataracts, decreased visual acuity, and synechiae. One of the most severe ocular complications remains the retinal vasculitis, which leads to a marked decrease in visual acuity, finally with irreversible blindness following retinal vascular occlusion or optic neuropathy [13–17].

Neuro-Behçet's disease (NBD) presents three patterns of neurological impairment, according to *International Consensus Recommendations*: central nervous system (parenchymal multifocal/diffuse, cerebral, optic neuropathy and non-parenchymal cerebral vein thrombosis, intracranial aneurysm, acute meningeal syndrome), peripheral nervous system (peripheral neuropathy, multiplex mononeuropathy, myopathy), and mixed, with parenchymal and non-parenchymal involvement [11, 18, 19].

From the therapeutic perspective, the resources remain the glucocorticoids and the immunosuppressants, selected cases being eligible for anti-tumor necrosis factor-alpha (TNF-α), anti-cluster of differentiation 20 (CD20) or interferon-alpha (IFN-α) agents [20, 21].

Case presentation

Patient, 36-year-old, smoker, with family history of alcoholic hepatic cirrhosis on the paternal line and stroke on the maternal line, was admitted to the Clinic of Rheumatology, Railways Hospital, Craiova, Romania, in November 2018, for recurrent-neglected oral aphthosis, left hip pain, recurrent *erythema nodosum*, reduced visual acuity of the right eye, weight loss about 8 kg in the last eight months, profuse sweating, marked fatigability.

Historically, are relevant: In 2016, the inaugural episode of *erythema nodosum*, remitted after the administration of nonsteroidal anti-inflammatory drugs, subsequently adding reduction of visual acuity of the left eye – with the establishing of diagnosis of optic neuropathy of the left eye and the initiation of corticotherapy (doses, types of drugs, duration unspecified and undocumented in 2016–2017). In October 2017, with persistent painful symptoms at the right coxofemoral joint, was diagnosed with avascular necrosis of the femoral head, being practiced femoral head drills in an Orthopedic Service. During the period January 2018–July 2018, based on the

persistence of the pain at the right hip, he was re-evaluated orthopedically and diagnosed with stage IV Chandler's disease, with the practice of a total arthroplasty not cemented hard–hard couple straight hip, with favorable evolution, but with a violent perioperative episode of oral aphthosis. Bio-humoral, significant non-specific inflammatory syndrome [erythrocyte sedimentation rate (ESR) 96 mm/h, respectively C-reactive protein (CRP) 18.2 mg/dl], as well as persistent leukocytosis [leukocytes – 17 000/mm^3 (January 15, 2018) and 24 500/mm^3 (January 22, 2018)] were detected.

Later, he was investigated in another Rheumatology Clinic in the country for the recurrence of *erythema nodosum*, without succeeding the etiological contextualization of it: antistreptolysin O, negative antinuclear antibodies, excluding a specific etiology. Excision of a dermal–hypodermal nodular lesion was performed, the histopathological (HP) examination being irrelevant for any specific pathology.

At a careful history and reinterpretation of the case in the Clinic of Rheumatology, in November 2018, recurrent episodes of oral aphthosis were identified (last, violent perioperative in July 2018), thus, with the assumption of BD, it was indicated the testing of the human leukocyte antigen-B51 (HLA-B51) allele, with a positive result. The ophthalmological evaluation revealed: optic neuropathy of the right eye, nevritic optic sequelae of the left eye, ophthalmoscopic examination of the right eye – reduced papillary edema, the papilla with clear contour. The biological balance revealed a thrombophilic-negative profile, cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), perinuclear (p)-ANCA – negative, with persistent inflammatory syndrome (CRP 15.692 mg/dL) and leukocytosis (leukocytes 13 800/mm^3). Diagnosis of BD HLA-B51 phenotype with severe bilateral optic neuropathy was formulated. Parenteral therapy with Methylprednisolone was administered intravenous (0.5 g in three consecutive days), then oral therapy with Prednisone (0.75 mg/kg/day), concurrently with oral administration of Imuran (100 mg/day), in combination with specific ophthalmological therapy (Maxidex and Tropicamide), with temporary cessation of visual acuity damage to right eye. During hospitalization, no febrile or subfebrile states, no recurrent oral aphthosis or *erythema nodosum* were reported.

In order to evaluate the therapeutic strategy specific to the neuropathy disorder, the patient was referred to a specialized Neuro-Ophthalmological Center, where, after excluding demyelinating diseases, such as multiple sclerosis [cerebral nuclear magnetic resonance (NMR) examination and cerebrospinal fluid analysis, without oligoclonal bands), the NBD diagnosis was reconfirmed and the combination of glucocorticoids and Azathioprine was maintained.

In February 2019, the ophthalmological reassessment identifies a discrete conjunctival hyperemia at the anterior bilateral pole, whereas, at the posterior pole: left eye – temporal papilla pale, arteries with wall taped to papillary emergence, thickened, venous loop at the bottom of the papilla (Figures 1, 4 and 5); right eye – papilla with papillary excavation, with cup-to-disc (C/D) ratio 0.4, arteries with wall taped to papillary emergence (Figures 2, 3 and 6).

The tomography underlined the degree of damage of the left eye, both macular and at the level of the optic nerve: retinal atrophy by retrograde atrophy of the nerve fiber layer, quasi-total papillary atrophy (Figure 7).

The established diagnosis was optic atrophy of the both eyes, respectively retrobulbar neuropathy of the left eye. It was recommended to continue the treatment with Prednisone and Imuran, with the addition of Gangliolife (1 tablet/day administration) and ophthalmological control at three months, in order to reassess the optic function.

The rheumatological reassessment, in July 2019, did not identify clinical, bio-humoral or imaging signs of disease progression and activity, as well as the absence of iatrogenic adverse reactions to the combined immunosuppressive therapy. As a result, it was decided to continue Azathioprine therapy and tapering for glucocorticoids.

Discussions

The case resulted in a necessary upgrade of the information that underpins the nosological classification and vascular features according to the 2012 *Chapel Hill Revised Criteria*, BD and Cogan syndrome being recognized as part of the group of vasculitis, with small arterial and venous vascular disease. The *International Criteria for BD Classification* for the confirmation of BD diagnosis is based on a scoring system including cutaneous–mucosal, ocular, genital, neurological and vascular manifestations. The positivity of the pathergy test is considered optional, but of interest, its presence being the element that can confirm an uncertain diagnosis (Table 1) [11, 22].

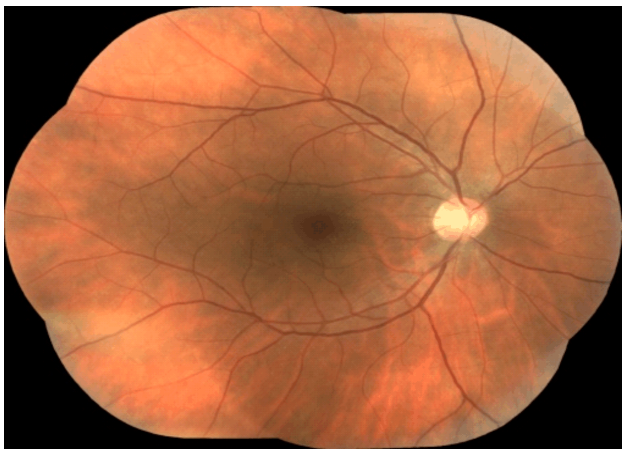

Figure 1 – ***Ophthalmoscopic exam: left eye.***

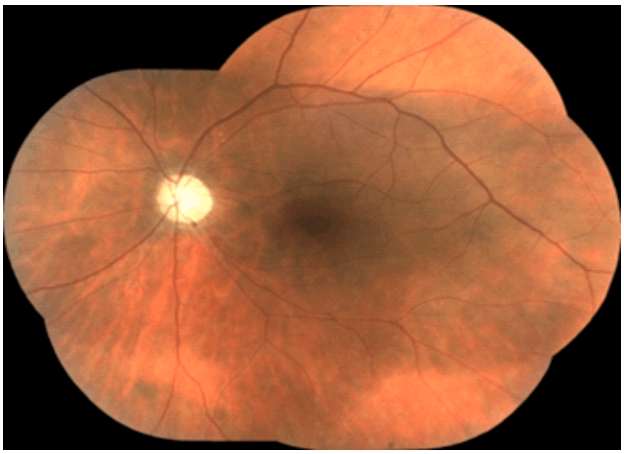

Figure 2 – ***Ophthalmoscopic exam: right eye.***

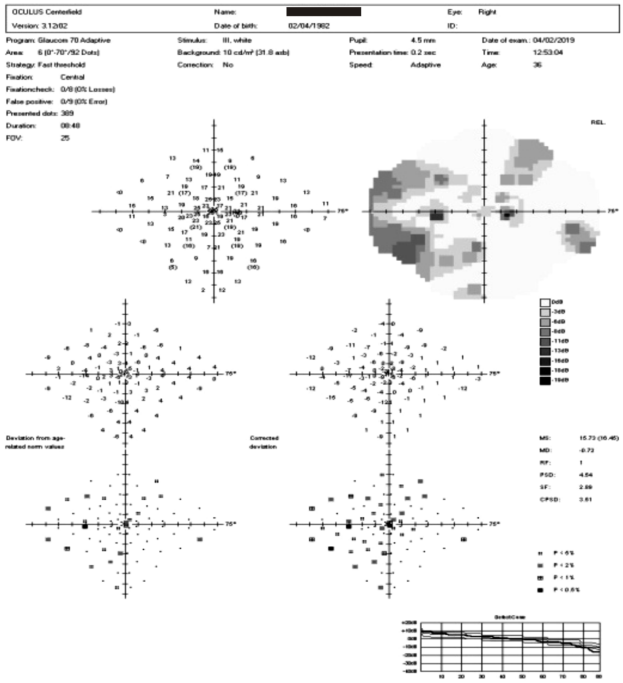

Figure 3 – ***Right eye, 70° perimeter: reduced limitation in the nasal sector.***

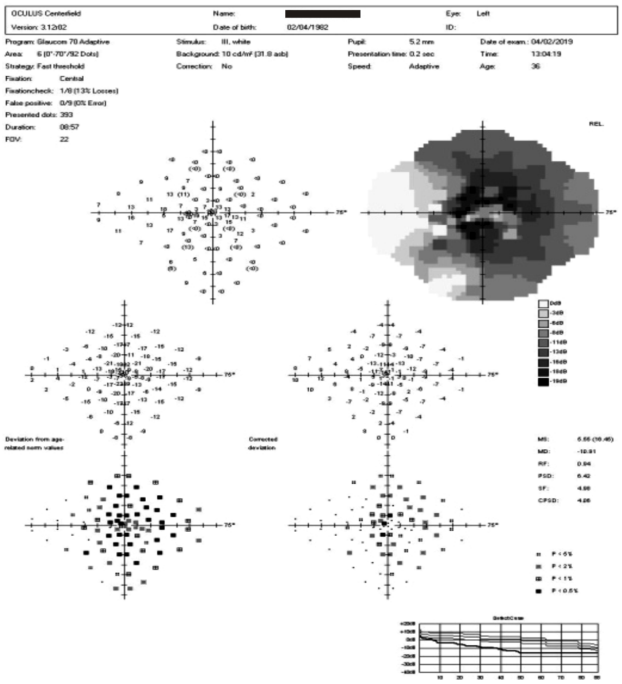

Figure 4 – ***Left eye, 70° perimeter: central perception island between 20° nasal, 10° upper and lower, 15° temporal, with good perception in the temporal sector beyond 30°.***

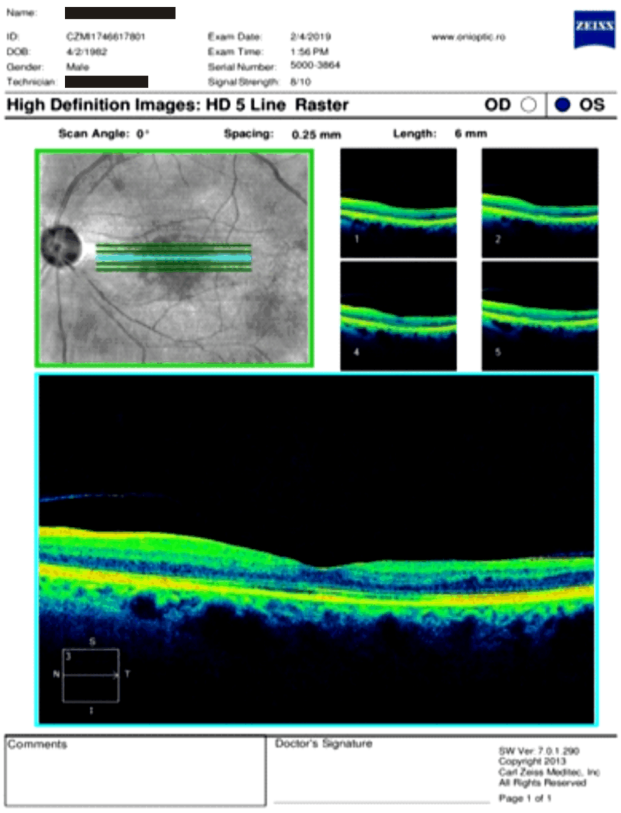

Figure 5 – ***Macula of the left eye (OS).***

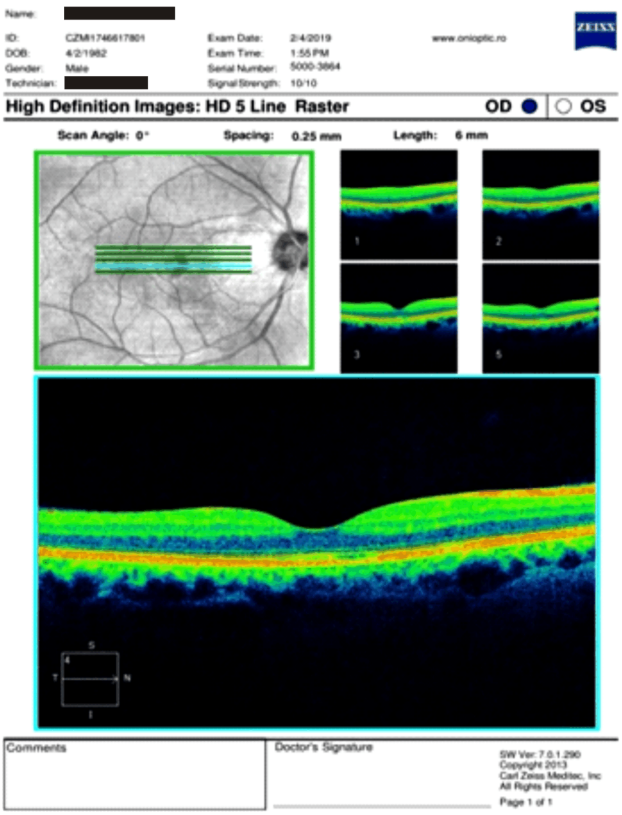

Figure 6 – ***Macula of the right eye (OD).***

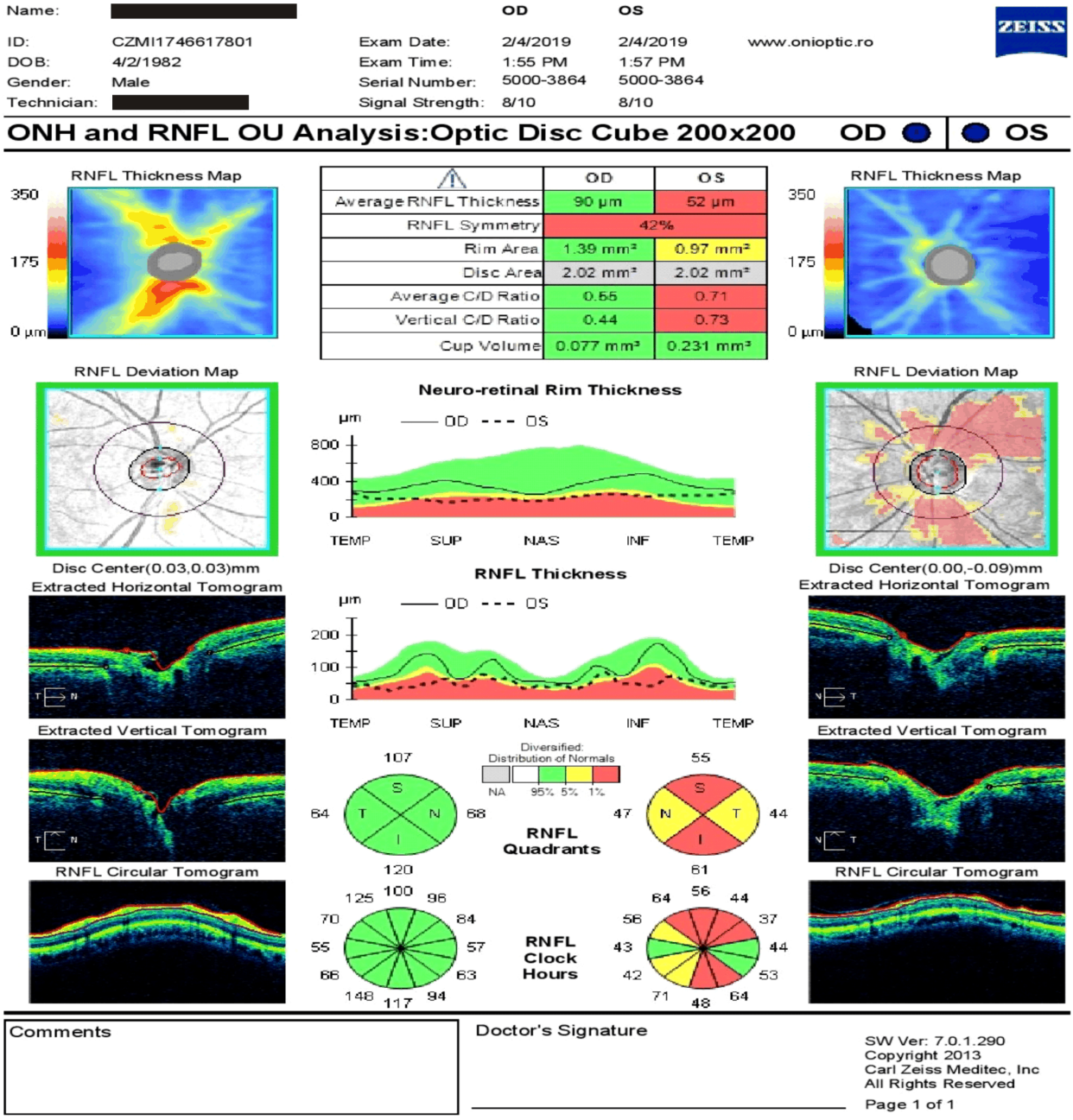

Figure 7 – ***Computed tomography of optic nerve. ONH: Optical nerve head; OD: Right eye; OS: Left eye; RNFL: Retinal nerve fiber layer.***

The pathergy reaction is the only test that fits the classification criteria for BD, but the sensitivity and specificity of the pathergy is higher in association with the HP elements compared to the clinical ones [23].

Table 1 – ***International Criteria for BD Classification 2014, point score system: scoring ≤4 indicates BD diagnosis [11]***

Symptoms	Points
Oral aphthosis	2
Genital aphthosis	2
Ocular lesion	2
Skin lesion	1
Neurological manifestation	1
Vascular manifestation	1
Positive pathergy test	1

BD: Behçet's disease.

According to the literature data, early HP changes are dominated by the abundance of polymorphonuclear cells in the inflammatory exudate, with the rapid development of leukocytoclastic vasculitis, neutrophilic vascular reactions and perivascular lymphocytic infiltrations. The main HP issue remains the presence of neutrophils in the test area, with or without the presence of other inflammatory cells [9, 24].

The last HP data [24] deepens the controversies, not being defined immunological mechanism interventions. Still, the main changes remain neutrophilic infiltrates in the test area (Table 2) [9].

In our case, the pathergy test was inconclusive due to possible prolonged corticotherapy.

According to the diagnostic criteria, the presented case was labeled as NBD, with a pattern of severe bilateral optic neuropathy, finding in the history and the picture of

the disease (recurrent oral aphthosis, *erythema nodosum* and neuro-ophthalmic touch), after exclusion of conditions such as Cogan syndrome. It may associate the presence of aortitis, arteritis, aortic aneurysms, but the clinical feature that differentiates it from BD is the absence of cutaneous mucosal damage, the patient presenting with recurrent episodes of oral aphthosis. Magic syndrome (oral and genital aphthosis, vasculitis and joint disorders) does not include neurological, gastrointestinal or pulmonary manifestations, whereas one of the three patterns of NBD is optic neuropathy, in this case being the main manifestation of disease. Negative testing of c-ANCA, p-ANCA and thrombophilic profile excluded the presence of ANCA-associated vasculitis but also of antiphospholipid syndrome [22].

Table 2 – ***An overview of the reported HP and immunofluorescence features of BD common mucocutaneous lesions [9]***

Mucocutaneous lesions	Reported HP features
Recurrent oral aphthae	Lymphocytes, macrophages, neutrophils, at the base of the ulcer, sometimes penetrating the epidermis, at the periphery
	Similar infiltrate at the perivascular regions in dermis fibrinoid necrosis of vessel walls (rare)
	Granular IgM and C_3 deposits in dermo-epidermal junction and in the perivascular regions (no immunoreactants deposits in RAS)
Genital ulceration	HP features similar to oral aphthae
Erythema nodosum-like lesions	Neutrophilic vasculitis
	Lymphocytic vasculitis
	Necrobiosis
	IgM deposits at the vessel walls
Pathergy reaction	Perivascular infiltrate of mononuclear cells
	Vasculitis (neutrophilic, leukocytoclastic) (+/–)
	Mast cells
	IgM, IgA and C_3 deposits
Papulopustular lesions	Intraepidermal pustules, spongiosis, neutrophil/ lymphocyte exocytosis, basal keratinocyte vacuolization
	Dermis edema, lymphohistiocytic/neutrophilic inflammatory infiltrate between collagen fibers and perivascular areas
	Vasculitis (+/–)
Thrombophlebitis	Thrombi in the vessel lumen
	Perivascular infiltrate of mononuclear cells

BD: Behçet's disease; C_3: Complement component 3; HP: Histopathological; IgA: Immunoglobulin A; IgM: Immunoglobulin M; RAS: Recurrent aphthous stomatitis.

NBD is one of the most serious manifestations in terms of multiple neurological damages, involving life risk. According to *International Consensus Recommendations*, the diagnostic criteria include: unanimously recognized classification criteria for BD, neurological syndrome proven to be caused by BD and demonstrated neuroimagically or by cerebrospinal fluid analysis, after the exclusion of other types of neurological disorders. Cerebral NMR remains the gold standard in the positive diagnosis of NBD, but also in the differential diagnosis with multiple sclerosis. Lesions in multiple sclerosis are located periventricularly, involving the internal capsule, whereas in NBD the impairment is usually subcortical, associated with atrophy of the brainstem [11].

In this case, the cerebral NMR excluded the presence of multiple sclerosis, a fact also supported by the results of the cerebrospinal fluid analysis.

NBD can occur in two forms: the vascular-inflammatory disease of the central nervous system, with parenchymal or non-parenchymal involvement, found in most patients, including the present case, and isolated venous sinus thrombosis with intracranial hypertension. The evolution of both forms is unpredictable, being needed future updates of therapeutic strategies [10, 19].

From the HP point of view, in the acute phase of NBD, it can be observed around the small vessels infiltrations with mononuclear cells, with the addition in the chronic one of numerous foci of dispersed neurons subjected to apoptosis, with formation of binucleated neurons. The specific HP image of NBD is represented by isomorphic glucose with viable neurons.

From the perspective of the patterns of systemic impairment, the data of five worldwide trials of BD are relevant (Iran, Japan, China, Korea and Germany), the most frequent manifestations being oral aphthosis, in 98% of cases, followed by ocular damage – 55%, 69%, 35%, 51%, and 53%, respectively, with increased frequency in male patients, with onset in the second or third decade of life. NBD was met in small proportions: 9%, 11%, 6.5%, 4.6%, and 11%, respectively [5].

Epidemiologically, the increased prevalence of BD cases in Turkey, Iran, Lebanon, Iraq, Jordan, Israel and Japan, with the predominance of male gender, as opposed to female predominance in Korea, China, United States and North America, is unanimously accepted. In United States, it was also supported by a retrospective study of a group of patients with BD in Minnesota, over a period of 45 years [25]. It should be noted that most of the disorders were of the cutaneous-mucosal type, with an equal incidence of ocular, vasculitic and neurological disorders, the prevalence of this disease being lower compared to the areas located along the old "silk road". On the other hand, another study carried out on a batch of 1527 patients with BD from Korea, over a two-year period, revealed the frequency of ocular damage and negative pathergy test, with an increased incidence in women. It is assumed that the positivity of the pathergy test is found especially in men, being considered a risk factor in evolution, in the case of our patient the result is inconclusive [7].

Data from the literature suggest a rare presence of optic neuropathy in BD. Relevant in this regard were two studies: Kidd reported 20 cases of optic neuropathy in patients with BD, of which half of the cases with unilateral involvement, in one-quarter of cases with sequential bilateral lesions. All patients showed favorable evolution under corticosteroids, without recurrence of neuropathy [26]. The second study, from 2015, targeted 440 patients with BD, out of which only 10 had inflammatory optic neuropathy and the rest various forms of ophthalmological impairments (panuveitis, anterior uveitis, posterior uveitis). Of those with inflammatory optic neuropathy, 20% progressed to definitive blindness, 40% to an improvement in ocular symptoms, and 40% remained stable [27, 28]. Our case is in the third pattern, patient having a stable evolution after the initiation of the associated treatment

with glucocorticoids and immunosuppressants, with no signs of progression of the disease.

Therapeutically, according to *European League Against Rheumatism* (*EULAR*) *Recommendations* 2018, both in the ocular and neurological disorders, corticotherapy and immunosuppressants (Azathioprine, Mycophenolate Mofetil, Cyclosporine, Cyclophosphamide and Chlorambucil), respectively IFN-α, are first line therapeutic options. Cyclosporine should be avoided in patients with BD, who associate optic neuropathy, because it may promote neurological damage [20].

Optic neuropathy is considered to be a manifestation of NBD and the therapeutic scheme must be modulated by taking this aspect into consideration. In cases refractory to combined therapy, anti-TNF-α agents (Infliximab, Adalimumab, Etanercept) may be used, but data from the literature are not supported by sufficient evidence from trials with significant numbers of patients demonstrating the risk–benefit relationship in the case of biological therapy, at least for NBD. Referring to the *International Criteria Recommendations* for BD of 2014, the most used anti-TNF-α agent remains Infliximab, the therapeutic experience with this being greater than the duration and groups of patients compared to other agents, followed by Adalimumab [21]. A therapeutic alternative may be represented by Rituximab, with favorable results being reported in a patient with NBD, with symptoms of intracranial hypertension, with tumor-like lesions evidenced by cerebral NMR and active vasculitis, without response to conventional glucocorticoid and immunosuppressive therapy. According to the authors, this case is unique, but of interest for the future, if Rituximab is proven effective in NBD cases refractory to the first-line therapeutic scheme [20, 29].

HLA-B51 is not a diagnostic criterion for BD, but its presence can influence the evolution of this disease. Thus, a study of 193 patients with BD, including NBD cases, revealed the presence of HLA-B51 in half of the cases, demonstrating that it can influence the installation of serious systemic disorders [30]. The relationship between this configuration and the increased frequency of cases of uveitis and *erythema nodosum* was demonstrated, the same aspect being supported by another study in a group of patients from Tunisia, where the absence of neurological and arterial aneurysms was noted in HLA-B51 positive patients [31]. In our case, the presence of the HLA-B51 allele was associated with bilateral neuro-ophthalmological impairment, which could confirm these data from the literature.

The evolution of BD remains unpredictable, numerous studies targeting the risk factors involved in the natural history of the disease. One such study published in 2011 included 412 patients with BD, monitored over the course of 16 years (July 1971–December 2007). The majority of patients were of Japanese origin, the prevalence being male, with an average age of 30 years old. It has been shown that male gender and the presence of HLA-B51 are predisposing factors for ocular impairment, which in turn can lead to a high frequency of neurological lesions [32].

One of the peculiarities of our case remains the necrotic femoral disease, interpreted as Chandler's disease – avascular necrosis of the femoral head. It should be noted that this is classified as primary or secondary, among the etiologies being high-dose corticotherapy. The etiological context of the avascular necrosis of the femoral head remains unraveled, given the probability of the competitive action of the iatrogenic factor (prolonged corticotherapy) and the vasculitic impairment specific to BD. It is expected that in the context of the current therapeutic program – corticotherapy at low doses, in combination with immunosuppressants –, similar structural damage may occur at other bone sites, involving specific imaging surveillance and reconsideration of the therapeutic strategy [33].

The evolutionary peculiarity of our case consisted of the nonspecific onset (*erythema nodosum*), with the rapid and violent addition of optic neuropathy and recurrent oral aphthosis, neglected therapeutically for several years, the case being part of the 11% cases reported in literature [5].

According to *EULAR Recommendations*, the patient was treated with corticosteroid and Azathioprin, having a stable evolution, with no clinical, bio-humoral or imaging signs of disease progression and activity.

Conclusions

NBD brings together ophthalmological disorders, with unpredictable prognosis and therapeutic response. Rapidly progressive optic neuropathy is one of the severe manifestations requiring a multidisciplinary approach. It is necessary to upgrade the therapeutic strategies specific to NBD patterns, which most often present a life risk.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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