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Central retinal vein occlusion : an uncommon complication in sarcoidosis

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Abstract

Sarcoidosis is a multi-system granulomatosis of unknown etiology, defined by the presence of epithelioid and gigantocellular granulomas, without caseous necrosis. Ocular sarcoidosis manifests mainly as bilateral granulomatous anterior uveitis. Occlusion of the central retinal vein in sarcoidosis is a rare manifestation, which is the particularity of our observation.

We report the case of a patient presenting with unilateral central retinal vein occlusion associated with granulomatous anterior uveitis on the same side. Systemic manifestations and further investigations led to the diagnosis of sarcoidosis.

Key words: Sarcoidosis; granulomatosis; central retinal vein occlusion, uveitis, lymphadenopathy.

What is new? What is important?

Occlusion of the central retinal vein is a rare ocular complication in sarcoidosis, and an exceptional revealing situation. We report the case of a patient presenting with a unilateral central retinal vein occlusion associated with granulomatous anterior uveitis on the same side and polyadenopathy, leading to the diagnosis of sarcoidosis. This unusual case highlights the importance of considering the diagnosis of sarcoidosis in cases of ocular involvement such as central retinal vein occlusion, and of looking for clinico-biological and histological elements to confirm it.

INTRODUCTION

Sarcoidosis is a chronic multisystem disease of unknown origin, characterized by the development of epithelioid granulomas without caseous necrosis in various body tissues [1]. The most frequent manifestations are pulmonary, cutaneous and ocular involvement.

Ophthalmological involvement occurs in 30–60% of patients with systemic sarcoidosis [2]. It is revelatory of the disease in 10–20% of cases [3].

The most frequent ocular manifestation of sarcoidosis is granulomatous anterior uveitis. Central vein occlusion has been reported exceptionally. We report an observation of central retinal vein occlusion (CRVO) during systemic sarcoidosis.

Observation:

A 45-year-old man, type 2 diabetic on oral antidiabetics, was admitted to hospital to investigate polyadenopathies that had been evolving for 6 months. On examination, the adenopathies appeared progressively in a context of apyrexia. They were associated with weight loss of 10 kg in one year, without asthenia or anorexia. The patient did not consume raw milk, had no contact with animals and was not infected with tuberculosis.

He also reported decreased visual acuity and bilateral visual blur, predominantly on the left side. On examination, there were cervical retroauricular, jugulocarotid, axillary and inguinal adenopathies of 1 to 3 cm in diameter, firm, mobile and painful, with no inflammatory signs. The rest of the examination was unremarkable. Ophthalmological examination revealed visual acuity of 6/10 on the right and very low on the right, limited to counting fingers at 4 metres, severe dry eye syndrome with bilateral superficial punctate keratitis and anterior uveitis of the left eye. Fundus examination, supplemented by retinal angiofluography, showed retinal patchy haemorrhages associated with occlusion of the central vein of the left retina (Figures 1 and 2).

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The blood count showed lymphopenia at 930/mm^3. There was no biological inflammatory syndrome. Liver, phosphocalcium and renal function tests were normal. Protein electrophoresis showed polyclonal hypergammaglobulinemia at 22.8 g/l. Conversion enzyme was elevated to 140 U/l (N:20–70). Infectious diseases were investigated. Serologies for hepatitis B and C, HIV (human immunodeficiency virus), EBV (Epstein-Barr virus), CMV (cytomegalovirus), Toxoplasmosis, Wright and Vidal were negative.Tuberculosis investigation was negative. A thoracic-abdominal-pelvic CT scan revealed a proliferation of supra- and subphrenic lymph nodes involving the cervical, axillary, hilar, mediastinal intra- and retroperitoneal and inguinal lymph nodes, associated with multinodular splenomegaly.

Lung parenchyma was healthy. Sternal puncture was normal. Lymph node biopsy and pathological examination revealed non-necrotizing granulomatous lymphadenitis with no evidence of malignancy (Figures 3, 4). Biopsy of the accessory salivary glands in search of a 2nd granuloma site revealed no abnormalities. In addition, due to central retinal vein occlusion, acquired and constitutional thrombophilia tests and Rickettsiosis serology were negative.

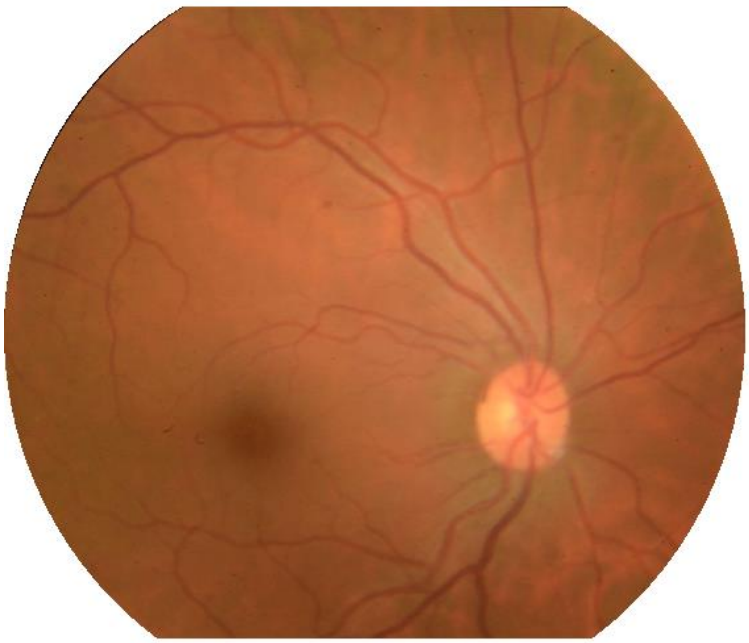


Figure 1. Fundus of the right eye: retinal hemorrhages in patches and flashes in all 4 quadrants, vascular dilatation and tortuosity, retinal edema of the posterior pole.

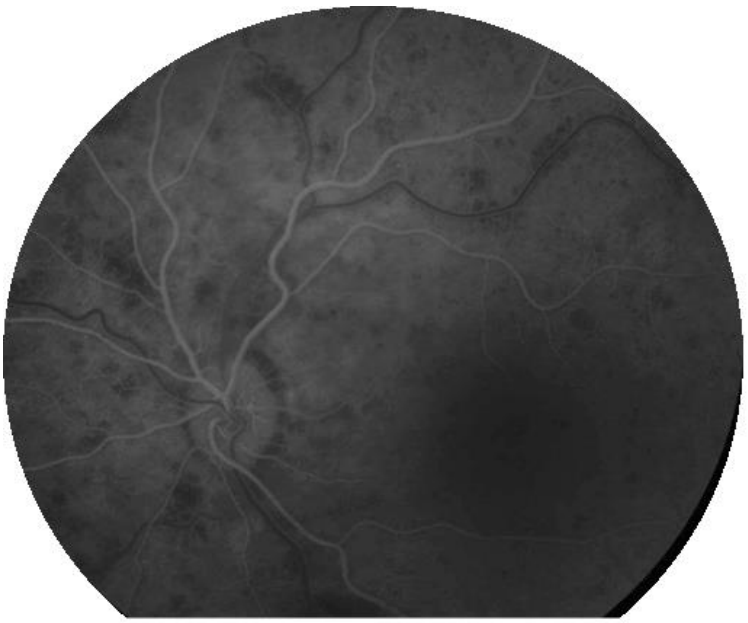


Figure 2. Fluorescein angiography of the left eye: lengthening of arteriovenous time to over 5 seconds Mask effect of hemorrhages, no diffusion and no peripheral ischemia.

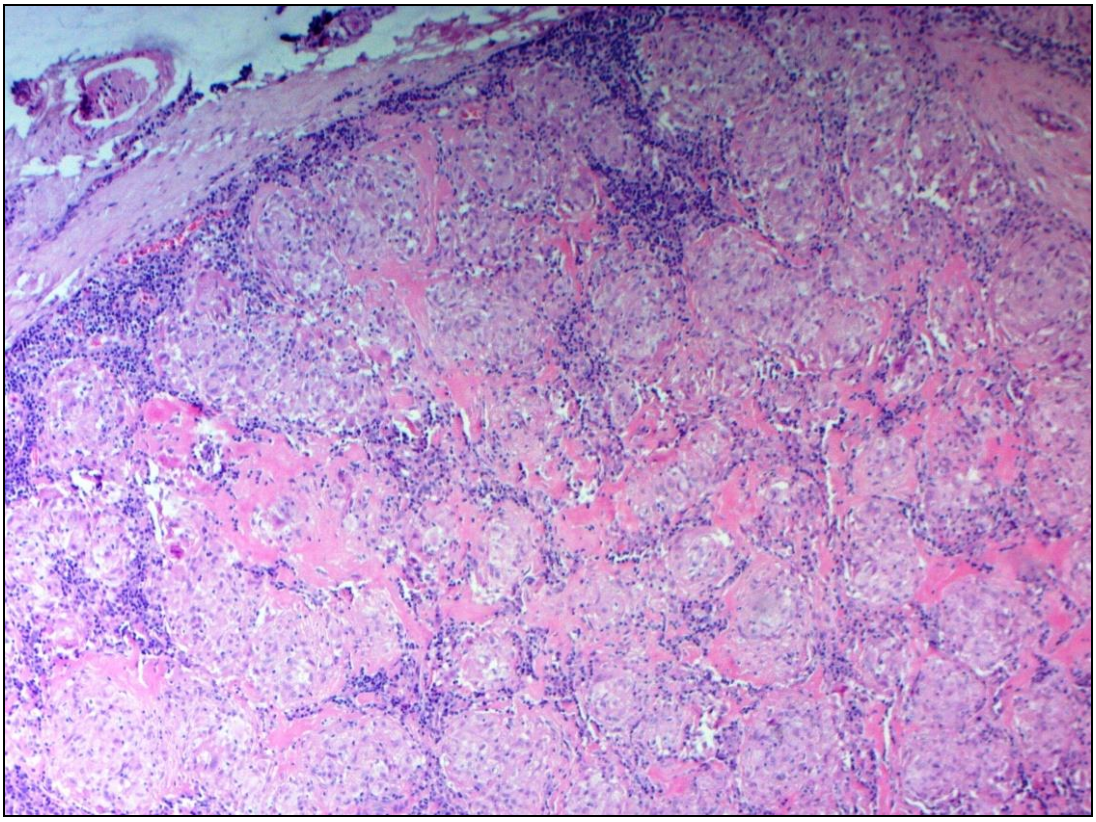


Figure 3. Presence of numerous non-necrotizing epithelioid granulomas replacing normal nodal parenchyma. These granulomas are focally surrounded by collagen fibers (hematoxylin eosin×50).

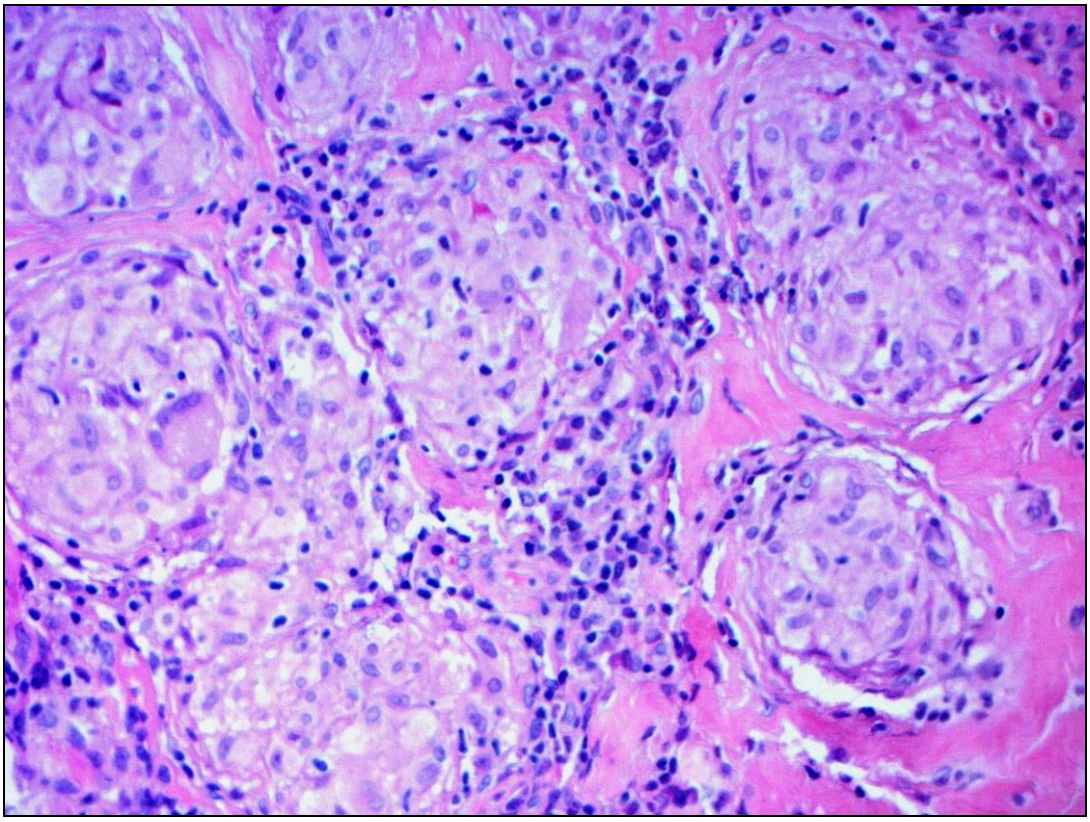


Figure 4. Presence of multiple granulomas composed of epithelioid histiocytes with rare multinucleated giant cells (hematoxylin eosin×200).

At the end of these investigations, the diagnosis of sarcoidosis was retained due to lymph node involvement with a granuloma appearance without caseous necrosis on histological examination of a lymph node biopsy, nodular splenomegaly, lymphopenia, elevation of the conversion enzyme to 2 times normal, polyclonal hyper-gamma-globulinemia, tuberculin anergy and ocular involvement consisting of severe objective dry syndrome complicated by superficial punctate keratitis, anterior uveitis and occlusion of the central vein of the left retina.

The patient was treated with high-dose corticosteroid therapy at 1mg/kg/day for an initial 6-week course, followed by gradual tapering to a maintenance dose of 10 mg prednisone equivalent per day, with prescription of local treatment for the dry eye syndrome. The evolution was marked by the total disappearance of superficial adenopathies, improvement in subjective visual acuity, disappearance of hypergammaglobulinemia (control gamma globulins at 8 g/l) and lymphopenia (lymphocytes at 1630 elements/mm^3) at 1 month of treatment. The follow-up ophthalmological examination showed an improvement in visual acuity to 10/10 on the right and 4/10 on the left, disappearance of uveitis but persistence of OVCR confirmed on follow-up retinal angiofluography.

DISCUSSION

Sarcoidosis is a chronic multisystem granulomatous disease of unknown origin. It is characterized by granuloma formation without caseous necrosis in the affected organs [1]. Diagnosis is based on a clinico-biological and radiological picture that is suggestive of the disease, combined with evidence of granuloma at one or more distinct biopsy sites, with other causes of granuloma ruled out [4].

Ophthalmological involvement is common in sarcoidosis, accounting for 30–60% of cases and revealing the disease in 10–30% of cases [5]. It occurs more frequently in women, with 2 peaks between the ages of 25 and 29 and 65 and 69 [6]. Uveitis is the most frequent ocular manifestation, observed in 20–30% of cases and dominated by granulomatous anterior uveitis, as in our patient [7]. A dry syndrome complicated by superficial punctate keratitis is reported in 15 to 30% of cases [8]. Posterior involvement is much rarer, manifesting as focal or nodular “candle-spot” periphlebitis localized at the posterior pole, associated or not with subretinal choroidal granulomas or cystoid macular edema. Rarer cases of CRVO in the setting of sarcoidosis have been reported in the literature in the form of isolated cases. Gass and Olson [9], Kimmel *et al.* [10], Denis *et al.* [11] and M. Momtchilova *et al.* [12] describe cases of unilateral CRVO in sarcoidosis very similar to our patient. A prospective Greek study of 50 patients with histologically proven pulmonary sarcoidosis on trans-branch biopsy, which investigated ocular manifestations during sarcoidosis, showed that 7 patients had CRVO [13]. CRVO frequently affects young men [14]. Its physiopathogenesis is an occlusive vasculitis of the central retinal vein, compression by a choroidal granuloma or retinal periphlebitis obstructing the central retinal vein.

Clinically, it presents as a painless drop in visual acuity with visual blur. These were the ocular complaints described by our patient. On the fundus, it generates segmental perivenous exudates seen as candle stains or a vascular sheath. The thrombosed vein appears on the fundus as a tortuous dilated vein. Retinal fluorescein angiography confirms CRVO and detects complications such as hemorrhages, exudates, areas of retinal ischemia or neo-vessels [12,14]. These findings were well demonstrated in our patient, apart from retinal ischemia and neo-vessels, which were absent.

Reported cases of CRVO in the context of sarcoidosis, as well as our patient, have in common lymph node involvement, with or without pulmonary parenchymal lesions, associated with elevated conversion enzyme. The histological diagnosis was based on the demonstration of a granuloma on an extra-ocular biopsy [11,12, 15,16].

Since biopsy is often not feasible in the absence of a suspicious lesion, new criteria have been established for the diagnosis of ocular sarcoidosis: the revised IWOS criteria, which have recently been the subject of an international consensus [17] and are based on: the presence of ocular signs suggestive of sarcoidosis, the elimination of other causes of granulomatous uveitis and the results of systemic investigations in favour of sarcoidosis. CRVO is not included in the diagnostic criteria for ocular sarcoidosis, given the rarity of this complication.

The standard treatment for ocular sarcoidosis is corticosteroid therapy, local in the case of involvement of the anterior segment of the eye and systemic in the case of involvement of the posterior segment or optic neuritis. Bolus doses of methyl-prednisolone are reserved for severe forms threatening visual prognosis. High doses of 1mg/kg/day

prednisone equivalent are often required at the start of treatment, followed by gradual tapering to a low dose of long-term corticosteroids. A 2nd-line immunosuppressive treatment may be discussed in cases of cortico-resistance or cortico-dependence. Antimetabolites (methotrexate, azathioprine, mycophenolate and leflunomide), T-cell inhibitors (cyclosporine and Tacrolimus) and alkylating agents (cyclophosphamide and chlorambucil) have most commonly been used for the treatment of uveitis. Among these agents, Methotrexate is the most widely used immunosuppressive therapy for ocular sarcoidosis [12,18]. Anti-TNFa, as a biological immunomodulatory agents have also been widely used for the treatment of sarcoidosis with uveitis as third line therapy, such as Adalilumab which showed a significant outcome. There is no codified treatment for CRVO. Reported cases have been treated with high-dose corticosteroids. Cases of retinal ischemia, persistent neovascularization or intravitreal hemorrhage may be treated with laser photo-coagulation [12].

Concerning the management of OVCR, the latest recommendations from the European Society of Retinal Specialists (EURETINA) specify the use of laser photocoagulation and vascular endothelial growth factor inhibitors (anti-VEGF). Anticoagulant treatment is not indicated in CRVO [19].

In a recent retrospective cohort study performed to evaluate the effectivness of antiplatelet and anticoagulant agents in 365 patients with CRVO, experts shouwed that the use of these agents is not associated with any CRVO structural outcomes [20].

Our patient was treated with high-dose oral corticosteroids for 6 weeks, followed by gradual tapering.

Although several cases of CRVO in sarcoidosis have evolved favorably on systemic corticosteroid therapy, the evolution in our patient was marked by improvement in visual acuity, disappearance of anterior uveitis but persistence of CRVO and retinal hemorrhages at 1 month of treatment, similar to the case reported by Hiraoka [16]. This may be explained by the delay between the onset of ophthalmic sarcoidosis and the start of systemic corticosteroid therapy, and underlines the importance of early diagnosis and management of ocular sarcoidosis [21].

Factors with a poor visual prognosis include [22]: advanced age, female gender; chronic disease course, posterior segment involvement, delay in management for more than a year, low initial visual acuity, peripheral retinal lesions, macular edema or glaucomatous neuropathy. Our patient had the following poor prognostic features: low initial visual acuity, posterior segment involvement; delayed management explaining partial visual recovery.

CONCLUSION

Unilateral CRVO in sarcoidosis is an exceptional ocular complication of this entity, which underlines the originality of our observation. The positive diagnosis of ocular sarcoidosis is sometimes difficult, particularly in the absence of clinico-radiological signs and histological evidence in favour. Posterior involvement is a poor prognostic factor, threatening the visual prognosis. Knowledge of this possible complication in sarcoidosis would enable rapid and appropriate management to improve functional prognosis and limit visual complications.

Sarcoidoza este o granulomatoză multisistemică de etiologie necunoscută, definită prin prezența granuloamelor epitelioide și gigantocelulare, fără necroză cazeoasă. Sarcoidoza oculară se manifestă în principal ca uveită anterioară granulomatoasă bilaterală. Ocluzia venei centrale a retinei în sarcoidoză este o manifestare rară, ceea ce este particularitatea observației noastre.

Raportăm cazul unui pacient care prezintă ocluzie unilaterală a venei centrale retiniene asociată cu uveită anterioară granulomatoasă pe aceeași parte. Manifestările sistemice și investigațiile ulterioare au condus la diagnosticul de sarcoidoză.

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