

Paraneoplastic Ocular Sarcoid-Like Reaction in the Setting of Metachronous Pulmonary Carcinoma

Reação Paraneoplásica *Sarcoid-Like* por Carcinoma Pulmonar Metácrono

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ABSTRACT

We describe a case of ocular sarcoid-like reaction (SLR) in the context of pulmonary carcinoma.

A 67-year-old man in remission of two previous lung carcinomas presented with bilateral granulomatous panuveitis, disc edema and yellowish lesions in the retina's midperiphery. Workup showed multiple hilar adenopathies, confirmed as non-necrotizing granulomas upon biopsy. Sarcoidosis with ocular involvement was assumed, but there was poor inflammation control with topical/systemic steroids. Pulmonology re-evaluation showed 2 new adenocarcinomas; the patient was started on chemo/immunotherapy. Six months later, there were no signs of inflammation, yielding the diagnosis of paraneoplastic ocular/ganglionic SLR.

SLR is an immune-mediated reaction with rare ocular involvement. This case is noteworthy as the ocular SLR was the first manifestation of the two new lung adenocarcinomas in a patient in remission from two previous lung carcinomas. Controlling inflammation in these cases is achieved through treatment of the underlying neoplasia.

KEYWORDS: Lung Neoplasms; Paraneoplastic Syndromes, Ocular; Sarcoidosis.

RESUMO

Apresentamos um caso de reação *sarcoide-like* ocular (SLR) associada a carcinoma pulmonar metácrono.

Um homem de 67 anos, em remissão de carcinoma pulmonar, desenvolveu panuveíte bilateral granulomatosa, com lesões amareladas na média periferia e edema do disco óptico. A avaliação sistémica mostrou múltiplas adenopatias hiliares, cuja biópsia confirmou tratar-se de granulomas não caseosos. Inicialmente, suspeitou-se de sarcoidose ocular, mas a inflamação mostrou-se resistente aos corticosteroides tópicos e sistémicos. Após reavaliação, foram identificados dois novos adenocarcinomas pulmonares, levando ao início de quimioterapia e imunoterapia. Seis meses depois, a inflamação resolveu, confirmando o diagnóstico de SLR ocular/ganglionar paraneoplásica.

A SLR é uma reação imunomediada rara com envolvimento ocular. Este caso é relevante pois a SLR ocular foi a primeira manifestação de dois novos adenocarcinomas pulmonares, sendo que o controlo da inflamação só foi possível com o tratamento da neoplasia subjacente.

PALAVRAS-CHAVE: Neoplasias do Pulmão; Sarcoidose; Síndromes Paraneoplásicas Oculares.

INTRODUCTION

Sarcoidosis, first described in the 18th century, is a multi-system disease mediated by helper T-cell lymphocytes, whose aetiology remains unknown. The disease is characterized by the infiltration of various organs by non-necrotizing epithelioid cell granulomas. Most cases occur between the ages of 25 and 40, and although individuals of all races can be affected, those of African or Scandinavian descent have a higher risk than Caucasians.¹ There is no gold standard or definitive criteria for diagnosing sarcoidosis, but clinicians typically rely on three key factors: consistent clinical and analytical presentation, histologic demonstration of non-caseating granulomas, and exclusion of other granulomatous disorders.²

Sarcoid-like reactions (SLR) refer to the development of non-necrotizing granulomas as part of an immune response, which may be triggered by various infections, drug exposure, or malignancy, in patients who do not meet the criteria for systemic sarcoidosis. Paraneoplastic SLRs have been reported in up to 20% of lymphomas and 4% of solid carcinomas.³ The exact pathophysiology of SLR is still unknown. Some authors⁴ suggest that SLR represents a T-cell-mediated immune response to tumour markers, though there is uncertainty in the published data regarding the survival prognosis of these patients.⁵

Ocular SLR in the context of a malignant tumour is exceedingly rare,⁶ with only a few cases documented in the literature. In this report, we present the case of a patient in remission from previous epidermoid lung cancer and adenocarcinoma, in whom ocular/ganglionic SLR preceded the diagnosis of two new lung adenocarcinomas.

CASE REPORT

Observational case report with description of the baseline clinical and demographic characteristics and relevant ancillary testing, as well as response to the outlined treatment.

This report was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for the use of their anonymized clinical information and relevant testing. The patient was fully informed of their right to withdraw consent at any stage.

A 67-year-old man presented to our emergency department in November, 2021, with complaints of painful red eye, floaters, and decreased visual acuity. His medical history was notable for hypertension and significant smoking habits, with over 40 pack-years and current use of 1 pack per day. His oncologic history included right-sided epidermoid lung cancer (staging: cT4N2M0), diagnosed in 2011 and treated with a combined regimen of chemotherapy and radiotherapy, as well as a metachronous right-sided pulmonary adenocarcinoma (staging: cT1aN0M0, with a negative Next Generation Sequencing panel), diagnosed in 2017 and treated with stereotactic body radiation therapy. Since the patient was asymptomatic and follow-up exams showed no

evidence of metastasis or local recurrence, he was considered to be in remission. He had no relevant ocular history.

Upon examination, his best-corrected visual acuity (BCVA) was 1/10 in the right eye (RE) and 4/10 in the left eye (LE). There was conjunctival hyperaemia, marked anterior segment inflammation (Tyndall 3+/flare 2+) with granulomatous keratic precipitates, moderate inferior vitritis, and yellowish chorioretinal lesions in the mid-periphery of both eyes. The right eye also showed optic disc edema.

Fluorescein angiography revealed multiple, punched-out, round lesions with early hypofluorescence and late hyperfluorescence. On indocyanine-green angiography, these corresponded to hypocyantescent choroidal lesions in the early and intermediate phases of the study. Additionally, there was capillary dropout in the retinal periphery without perivascular leakage suggestive of vasculitis. Both eyes optic nerves also demonstrated leakage throughout the exam (Fig. 1). There was no evidence of cystoid macular oedema on either fluorescein angiography or macular optical coherence tomography (OCT).

Initial systemic workup, including angiotensin-converting enzyme levels and HLA-A29 testing, was negative for infectious or inflammatory disorders. The patient was started on topical dexamethasone and systemic prednisolone (1 mg/kg/day) with a prolonged tapering regimen.

Given that the ocular phenotype closely resembled that of sarcoidosis panuveitis, evaluation by the assistant pneumologist was required. Multimodal imaging was required, showing no new lung nodules suspicious of neoplasia in both the computed tomography (CT)-scan or PET-FDG; however,

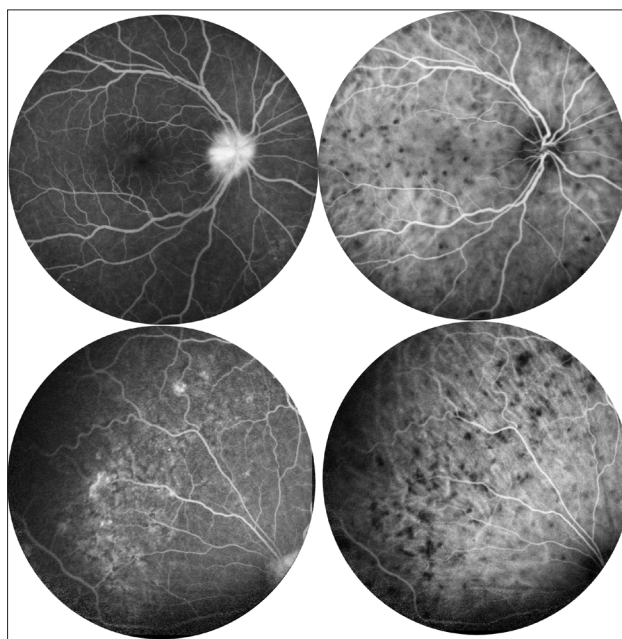


Figure 1. Late phase of fluorescein angiography (FA) and intermediate phase of indocyanine-green angiography (ICG) of the right eye (top) and left eye (bottom) reveal numerous hyperfluorescent round lesions in the FA, with corresponding hypocyantescent lesions in the ICG, indicative of active chorioretinitis. In the right eye, optic disc leakage is evident. The left eye images demonstrate capillary dropout and peripheral retinal ischemia.

multiple bilateral hilar and mediastinal adenopathies were identified, and endobronchial ultrasound biopsy showed non-necrotizing granulomas, with no evidence of malignancy. A bronchoalveolar lavage was also performed, showing 33% lymphocytes with a predominance of CD4+ (CD4/CD8 ratio – 2.8); evaluation for malignant cells was negative.

A diagnosis of sarcoidosis with ocular and ganglionic involvement was assumed. Despite treatment with systemic and topical steroids, there was poor control of the inflammation, especially in the RE, which maintained significant and refractory vitritis. One year after the initial diagnosis of sarcoidosis, the RE developed an inflammatory peripapillary neovascular membrane, which showed good response to 2 monthly intravitreal bevacizumab injections, with resolution of the intraretinal and subretinal fluid (Fig. 2). Given the previous oncologic history, and after consulting with the assistant pulmonologist, the patient was not considered a candidate for systemic immunomodulation. Consequently, a long-acting intravitreal corticosteroid implant (fluocinolone acetonide - Iluvien®) was performed in the RE, leading to reduced anterior and intermediate inflammation, while maintaining activity of the chorioretinal lesions. The patient was then scheduled for a follow-up pulmonologist appointment.

Further imaging, in 2023, revealed several bilateral lung nodules in the thoracic CT, and biopsy confirmed 2 left pulmonary adenocarcinomas. Genetic testing of the first showed PD-L1 <5%, *BRAF V600E* mutation, and positive RET-fusion; the second showed PD-L1 50%-69% and *KRAS G12C* mutation. These tumours were unrelated to the previous adenocarcinoma. Given the large number of bilateral nodules, not considered radically treatable, the patient was started on a chemotherapy plus immunotherapy regimen, achieving excellent disease control.

Six months after the initiation of chemo/immunotherapy, BCVA was 10/10 in the RE and 8/10 in the LE. There were no signs of anterior or intermediate inflammation or optic disc oedema in either eye; OCT did not show intraretinal or subretinal fluid that might indicate activity of the neovascular membrane of the RE. Fluorescein and indocyanine-green angiography revealed atrophic punched-out lesions with no signs of active vasculitis or chorioretinitis (Fig. 3).

Given the excellent response of the inflammation to the chemo/immunotherapy, a diagnosis of SLR with pulmonary lymph node and ocular involvement was established.

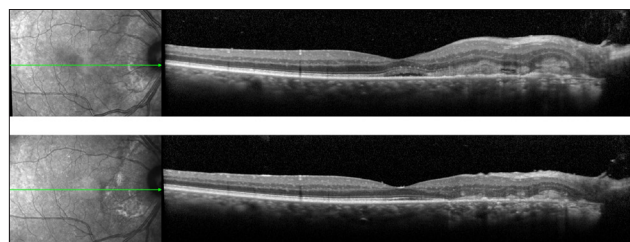


Figure 2. Macular OCT of the right eye, before (top) and after (bottom) two monthly intravitreal bevacizumab injections, showing a clear reduction in retinal thickness and subretinal hyperreflective material in the peripapillary area. There is no evidence of intra- or subretinal fluid in the post-treatment OCT.

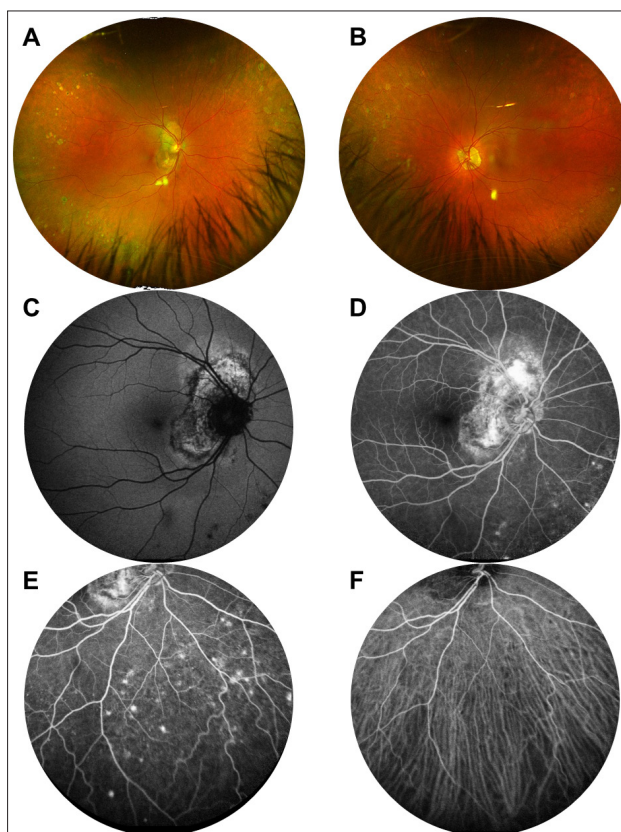


Figure 3. Multimodal imaging analysis 6 months after initiation of chemo/immunotherapy. A and B – Optomap images showing round, yellowish, punched-out atrophic lesions in the mid-periphery of both eyes. Atrophic pigmentary changes are also visible in the peripapillary region of the right eye. C and D – Autofluorescence and late-phase fluorescein angiography (FA) of the peripapillary changes of the RE. There are alternating areas of hypo- and hyperautofluorescence in C, and hypo- and hyperfluorescence in D, without leakage, indicating no activity of the peripapillary neovascular membrane. There is no optic nerve leakage. E and F – FA and indocyanine green angiography (ICG) of the round lesions seen in A. FA shows hyperfluorescence spots without corresponding hypofluorescence on ICG, suggesting inactive chorioretinitis lesions.

DISCUSSION

Sarcoid-like reactions refer to the development of non-caseating granulomas in patients who lack criteria for systemic sarcoidosis. Paraneoplastic SLR, per definition, occurs due to the development of said granulomas, in a remote location from the malignancy and that may not be attributed to the direct or metastatic invasion of the involved tissue. Such immune-mediated responses may occur before, at the same time of diagnosis or following treatment, sometimes years after initial detection, as this paper accurately demonstrates.⁷ Non-ocular SLR occur in up to 20% of hematologic and 4% of solid cancers and the non-necrotizing granulomas typically occur adjacent to the primary tumour, in the hilar/mediastinal lymph nodes, or localized only to the skin, without the systemic reaction commonly seen in systemic sarcoidosis.^{8,9}

Ocular involvement in SLR is exceedingly rare. Balasubramaniam *et al*¹⁰ described 5 cases of biopsy-confirmed

SLR with ocular involvement. In two cases, the ocular findings followed the diagnosis of malignancy - B-cell chronic lymphocytic leukemia and endometrial cancer - with the latter case also presenting with pulmonary hilar adenopathy and skin lesions. In two other cases, the SLR led to the diagnosis of the malignancy - mucosa-associated lymphoid tissue and renal cell carcinoma. Notably, one case involved both uveal melanoma and renal cell carcinoma. The main ocular findings in these cases were persistent follicular conjunctivitis, vitritis, chorioretinitis and vasculitis.

Regarding hematologic malignancies, Salman *et al*¹¹ reported a large case series of 4209 patients with chronic lymphocytic leukemia, with 8 patients having ocular SLR. In one case, the ocular involvement preceded the diagnosis; in the remaining 7 cases, ocular SLR developed at a mean of 49.7 months after the systemic diagnosis. Marlow *et al*¹² described a case of ocular SLR following the diagnosis of neuroendocrine tumour of the rectosigmoid colon.

The latest report, as of August 2024, by Casado *et al*,⁶ closely mirrors our case. It is the only other instance where SLR presented with both ocular and pulmonary lymph node involvement, preceding the biopsy-proven diagnosis of adenocarcinoma.

Several characteristics make our case unique and particularly noteworthy. It is 1 of four^{6,10,11} cases in which the ocular SLR preceded (in this case, by two years) and led to the diagnosis of the systemic malignancy, and the only reported instance where the ocular SLR preceded the diagnosis of two new adenocarcinomas in a patient under close follow-up and thought to be in clinical remission (since 2017). Additionally, only one other case¹⁰ was associated with macular neovascularization, although the treatment regimen for said neovascularization is not reported.

Treatment of paraneoplastic SLR is based on managing the underlying malignancy.⁶ To control the ocular inflammatory component, a regimen similar to sarcoidosis may be employed,¹³ which acts as a provisional measure while systemic treatment of the malignancy ensues. Caution must be taken as further immunomodulation may not be advisable.¹⁴ In our case, the panuveitis in the RE did not show a sufficiently favourable response to the topical and systemic steroid course. Given the past oncologic history, and after consultation with the attending pneumologist, a decision was made not to pursue further systemic immunomodulation. Treatment options for such cases are limited. Intravitreal fluocinolone acetonide (Iluvien®) is a long-acting intravitreal, non-bioerodible implant that provides a steady release of fluocinolone into the vitreous for up to 3 years, and is approved in Europe for use in non-infectious uveitis.¹⁵ In our case, the Iluvien® implant ensured good control of the anterior and intermediate uveitis with no ocular side effects. The chorioretinal lesions showed no improvement, a pattern that is in accordance with the available literature,¹⁶ and complete control of the inflammation was only achieved after initiation of the chemo/immunotherapy.

In conclusion, this report underscores the importance of considering paraneoplastic SLR in patients with a suggestive history presenting with panuveitis and sarcoidosis-compatible lesions. A multidisciplinary approach to these

cases is key, and ophthalmologists should thoroughly re-evaluate the initial diagnosis when the disease course deviates from the expected pattern.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

PM: Conceptualization, drafting of the text, sourcing and editing of investigation results, and critical revision for important intellectual content.

JC, CF, AB, SF: Critical revision for important intellectual content.

All authors approved the final version to be published.

PM: Conceptualização, redação do texto, obtenção e edição dos resultados da investigação e revisão crítica do conteúdo intelectual importante.

JC, CF, AB, SF: Revisão crítica do conteúdo intelectual importante.

Todos os autores aprovaram a versão final a ser publicada.

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