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Case Report

Multiphasic and multifocal cryptococcal immune reconstitution inflammatory syndrome in an HIV-infected patient: interplay of infection and immunity☆

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SUMMARY

We report a case of cryptococcal immune reconstitution inflammatory syndrome affecting the lungs, and 10 months later the cervical lymph nodes, in the absence of cryptococcal meningitis, in advanced HIV infection. Our report demonstrates the organ-specificity of the timing of the inflammatory response and illustrates the organ-specific interplay of immunity and infection in cryptococcal disease.

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1. Introduction

Cryptococcal immune reconstitution inflammatory syndrome (IRIS) is a monophasic illness that presents as 'paradoxical IRIS' in patients with diagnosed cryptococcal disease, or as 'unmasking IRIS' in patients who present with a first episode of cryptococcal disease after starting antiretroviral therapy (ART).[1] It usually affects the meninges, manifesting itself as cryptococcal meningitis. Here, we report a patient who developed a multiphasic and multifocal cryptococcal disease over a period of 2 years, involving lungs and lymph nodes, without meningeal involvement.

1.1. Case report

A 40-year old patient with known HIV infection presented with a 2-month history of cough and malaise. He had not been on ART for 10 months. His CD4 count was 80/μl (normal range 700–1200/μl). Thoracic computed tomography (CT) showed a consolidation in the left upper lobe. Bronchoalveolar lavage (BAL) and blood cultures did not grow any microorganisms. Tests for *Pneumocystis jirovecii* (immunofluorescence and PCR) and *Mycobacterium tuberculosis* (PCR and cultures) were negative. The cryptococcal antigen titer in serum was 1:128. Lumbar puncture including India ink examination and fungal cultures, revealed no pathological findings. The patient was started on antifungal therapy with liposomal amphotericin B. He improved and discharged himself on day 14 against medical advice. He continued on ART consisting of tenofovir/emtricitabine, darunavir/ritonavir, and maraviroc, as well as fluconazole.

The patient presented 12 months later with a 2-month history of cough, intermittent fevers, night sweats, and malaise. The CD4 count was 320/μl and his viral load was undetectable. A thoracic CT scan revealed a round central pulmonary nodule in the left lung, which was initially considered to represent a pulmonary

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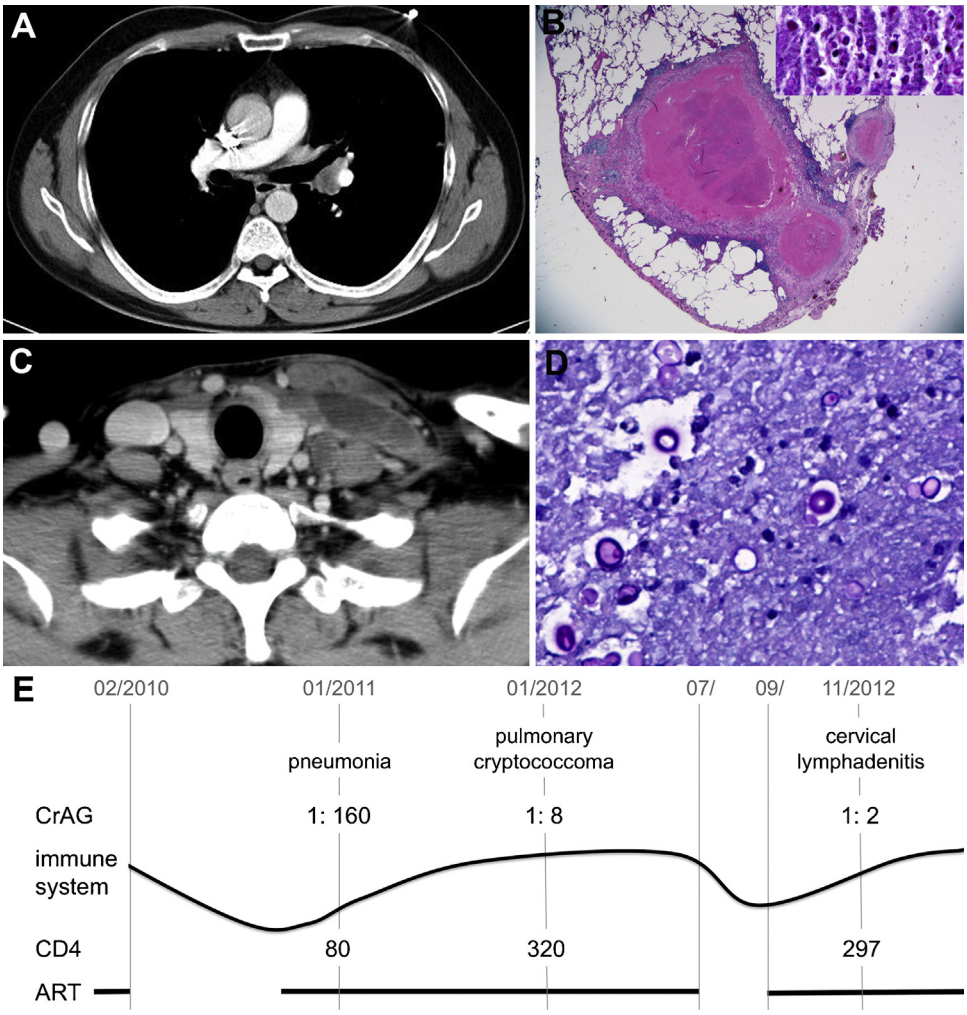

Figure 1. (A) Enhanced CT showing a central nodular mass in the left lung located between the upper lobe bronchus and the segmental bronchus. (B) Lung specimen showing three granulomas in the alveolar tissue surrounded by thickened pleura (hematoxylin and eosin stain, original magnification ×25); inset: high-power field examination of the granuloma, showing numerous yeast-like structures (periodic acid-Schiff (PAS) stain, original magnification ×400). (C) Contrast-enhanced CT scan of the neck at the level of thyroid gland, showing enlarged left cervical lymph nodes with ring-enhancement and central areas of low attenuation necrosis. (D) Left cervical lymph node histology showing numerous encapsulated yeast-like structures on PAS stain (original magnification ×400). (E) Time course of clinical manifestations, cryptococcal antigen titer in serum (CrAG), antiretroviral therapy (ART), and CD4 cell count (in cells/μl).

malignancy (Figure 1A). BAL revealed no growth, and blood cultures and lumbar puncture were negative. The cryptococcal antigen titer in serum was 1:16. Thoracoscopic resection of the lesion was performed. Histological examinations revealed multiple granulomas with numerous periodic acid-Schiff (PAS)-positive yeast-like structures (Figure 1B), but there was no growth of any bacterial or fungal microorganisms. The patient was started on combination therapy of liposomal amphotericin B and 5-flucytosine for 14 days, as well as prednisolone 0.5 mg/kg bodyweight with rash tapering. He was discharged clinically well on oral fluconazole (400 mg daily). Four months later the patient stopped his ART and antifungal therapy. He re-started ART after a 2-month break. Three months after the re-introduction of ART he presented with a painful swelling on his neck. His temperature was 38.2 °C. There was a tender left-sided supraclavicular mass. A contrast-enhanced CT scan of the neck showed extensive left cervical supraclavicular lymphadenopathy (Figure 1C). Fine-needle biopsy revealed necrotic areas with yeast-like structures identified on PAS stain (Figure 1D). Fungal cultures from the lymph node biopsy were negative. The cryptococcal antigen titer in serum was 1:2. His CD4 cell count was 297/μl and his viral load was undetectable.

A 2-week course of liposomal amphotericin B and 5-flucytosine with prednisolone 1 mg/kg bodyweight was repeated, followed by fluconazole maintenance therapy with rash tapering of prednisolone. At the 4-week follow-up, there was a reduction in the swelling both on clinical examination and CT imaging. At the 4-month follow-up, there was complete resolution of the clinical and radiological lesions. Retrospective DNA extraction from formalin-fixed paraffin embedded (FFPE) tissue samples from the lung and cervical lymph nodes revealed fungal DNA in the lung but not in the lymph nodes. The fungal DNA was identified as *Cryptococcus neoformans* var. *grubii* by a microarray developed for *Cryptococcus neoformans* and *Cryptococcus gattii*, which is based on the IGS region of rDNA.

2. Discussion

After presumed cryptococcal pneumonia, our patient suffered from two episodes of inflammatory manifestations of cryptococcal disease: first, a pulmonary nodule, and 10 months later, a cervical lymphadenitis. Pulmonary nodules and cervical lymphadenitis are rare but documented presentations of cryptococcal immune reconstitution syndrome.[1,2] According to the recently proposed definition of cryptococcal IRIS, both episodes can be classified as 'paradoxical IRIS':[3] they occurred after initiation of ART, the cryptococcal cultures were negative, and there was a significant

decrease in cryptococcal antigen titer (from 1:128 at the time of presumed cryptococcal pneumonia to 1:16 at the time of pulmonary nodule and then 1:2 at the time of cervical lymphadenitis). At the same time, the second episode of immune reconstitution 'unmasked' the Cryptococcus-associated disease at a different site.

To our knowledge, this is the first report of a multiphasic and multifocal cryptococcal IRIS in the absence of cryptococcal meningitis. Our case illustrates how persisting cryptococcal antigen triggers an inflammatory response every time the immune system is reconstituted by ART (Figure 1E). Interestingly, during the first episode of inflammation targeted against cryptococcal antigen in the lung, there was no inflammation of cervical lymph nodes. The latter occurred only during the second attack of IRIS. The dissociation of both events raises the question if the quality of the immune response following immune reconstitution differs between lung and lymph nodes. Of note, the most common form of Cryptococcus IRIS, cryptococcal meningitis, commonly occurs early after initiation of ART in a time frame where intrinsic control of an exaggerated immune response is limited.[4] In contrast, Cryptococcus IRIS in the lymph nodes usually represents a delayed reaction.[2]

According to the current theory, the key event of IRIS is a failure to clear antigen during the early phase of immune recovery, followed by an uncontained response to this persistent antigen during immune reconstitution.[5] IRIS is increasingly being considered not just an acute event, but a developing process with distinct immunological phases that evolve pathologically long before an IRIS event occurs clinically.[5] Our cases support this notion of IRIS as a prolonged immunological process with 'flare-ups' triggered by ART-associated improvement in immune status. Our patient benefited from anti-inflammatory therapy with steroids. However, with each episode we started antifungal treatment, as an active infection with Cryptococcus could not be ruled out pending culture results.

In conclusion, the organ-specific inflammatory response in cryptococcal IRIS has not yet been addressed in the literature. Further prospective studies with special emphasis on delayed IRIS affecting the lungs and lymph nodes are needed.

Conflict of interest: The authors report no conflict of interest.

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