A Neck Abscess One Year after Mycobacterial Infection in a Patient with Human Immunodeficiency Virus: A Diagnostic Dilemma

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Immune reconstitution inflammatory syndrome represents an exuberant inflammatory reaction to either previously unrecognized or recognized and treated infections as a result of restoration of the debilitated immune system. Clinical presentations associated with tuberculosis-induced IRIS include worsening of lymphadenopathy, splenic abscess, arthritis or osteomyelitis, worsening of pulmonary infiltrates, and parotitis [1]. Tuberculosis-IRIS typically occurs within 120 days of the initiation of highly active antiretroviral therapy.

We present a case of very late-onset IRIS in a human immunodeficiency virus-infected patient that manifested as suppurative cervical lymphadenopathy with osteolytic and splenic lesions. The symptoms began 13 months after initiation of HAART and TB treatment for lymph node and pulmonary mycobacterial infection and responded promptly to steroid treatment. One of several lymph node biopsies was positive on Warthin-Starry stain, raising the possibility of Bartonella co-infection.

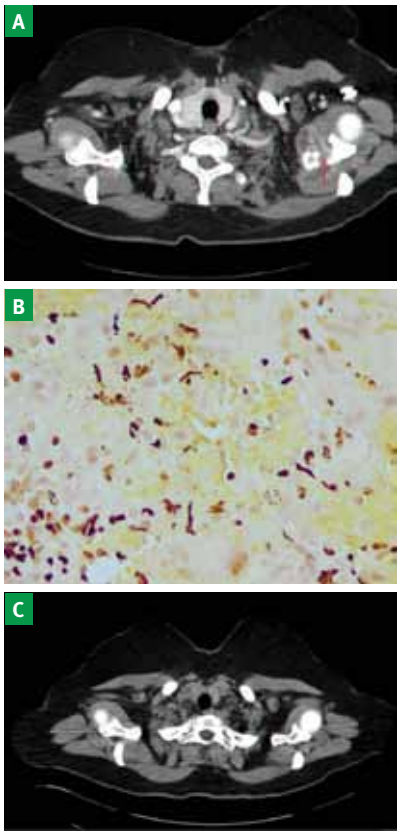
IRIS = immune reconstitution inflammatory syndrome
HAART = highly active antiretroviral therapy
= tuberculosis

PATIENT DESCRIPTION

A 52 year old Indian-born HIV -positive woman was admitted for investigation of a painful neck mass on 10 October 2006. She denied fever and weight loss and reported no recent travel or pet exposure. The patient was afebrile and physical examination was notable for a large tender mass of coalesced lymph nodes in the left suprascapular region. Her CD4 count was 382 cells/μl and viral load was undetectable. Computed tomography of the chest and abdomen demonstrated an abscess extending from C4 to the base of the left neck, as well as diffuse cervical lymphadenopathy, destruction of the supraspinatus, and a lytic lesion in the left scapula involving both sides of the bone suggestive of osteomyelitis [Figure A]. The lung fields were clear, the liver was normal, but numerous diffuse hypodense splenic lesions were observed. A left supraclavicular lymph node excisional biopsy was performed 2 days after admission. Bacterial and fungal cultures, mycobacterial stain and culture, periodic acid-Schiff, methenamine-silver, Giemsa stains and immunostains for Epstein-Barr virus and cytomegalovirus from the biopsy were negative. Elective scapular biopsy performed one month later revealed marrow and bone necrosis

HIV = human immunodeficiency virus

[A] Chest CT from October 2006 shows a lytic process penetrating the cortex of the spina-scapula (arrow). Collections with liquification are seen in the surrounding soft tissue
[B] Cervical lymph node biopsy from January 2007: A Warthin-Starry stain demonstrates the presence of organisms consistent with Bartonella. (x360)
[C] Chest CT from June 2008 shows the disappearance of the soft tissue findings with a residual small subchondral erosion in the scapula



with no granulomas, no acid-fast bacilli, and no evidence of tumor.

Thirteen months earlier, on 20 August 2005, the patient had been diagnosed with HIV (viral load 1.5 x 10^6 copies/ml) and TB that presented as fever, weight loss, bilateral supraclavicular, axillary and cervical lymphadenopathy. Acid-fast stain and tuberculosis culture from both lymph node and gastric aspirate were positive. The isolates were sensitive to all first-line TB agents. At diagnosis, CT of the chest and abdomen showed bilateral supraclavicular and axillary lymphadenopathy, clear lung fields, an enlarged liver, and few hypodense lesions in the spleen. Antiretroviral treatment with efavirenz, zidovudine and lamivudine was initiated, and TB treatment consisted of isoniazid, rifampin, pyrazinamide, ciprofloxacin, and vitamin B6. Cotrimoxazole was administered three times a week for *Pneumocystis jerovecci* prophylaxis due to a CD4 count of 95 cells/µl.

Eight days after the initiation of TB treatment the patient was readmitted due to weakness and right upper quadrant abdominal pain. Drug-induced hepatitis (aspartate aminotransferase 702 U/L, alanine aminotransferase 369 U/L, bilirubin 12.2 mg/dl) and anemia (hemoglobin 9.1 mg/dl) were diagnosed. Treatment with efavirenz was discontinued and replaced by ritonavir-boosted lopinavir. Stavudine replaced zidovudine and cotrimoxazole was temporarily withheld due to anemia. Treatment with rifampin, pyrazinamide and isoniazid was stopped. Streptomycin and ethambutol were added to ciprofloxacin and continued for 12 months. The patient's liver functions promptly normalized. She was completely asymptomatic until the appearance of the neck mass which prompted the current admission 13 months after the HIV/TB diagnosis.

Despite the negative acid-fast smear from the lymph node and later negative culture from the lymph node and scapula, on 12 October 2006 TB therapy with pyrazinamide, ethambutol, amikacin, ciprofloxacin and clarithromycin was instituted to treat a possible recurrence of sub-optimally treated tuberculosis. A repeat lymph node biopsy was performed in January 2007 due to the non-resolving cervical mass and yielded numerous rod-like bacilli on Warthin-Starry stain probably consistent with Bartonella [Figure B]. Molecular identification testing of the lymph node biopsy using 28S rRNA for fungi, two fragments for 16S RNA for bacteria including Bartonella, heat shock protein-65 for Actinomycetes, a specialized fragment between the genes 16S and 23S rRNA for mycobacteria as well as IS 6110 specific for *Mycobacterium tuberculosis*, were all negative after being performed twice. A final lymph node biopsy was performed in May 2007 due to persistent painful neck swelling and CT showing lymph nodes with central liquefaction in both the posterior and anterior left neck triangles. Bacterial and mycobacterial cultures from the biopsy were sterile and fragments of tissue showing inflammation were the only histological findings. Notably, special stains including Warthin-Starry were negative. At this time, the presumed diagnosis was late IRIS and the patient was prescribed prednisone 60 mg/day.

On follow-up one month later her prolonged neck swelling had resolved and CT revealed minimal lymphadenopathy. Her steroid treatment was gradually tapered down, with complete resolution of symptoms. Follow-up CT one and three years later demonstrated near-complete resolution of the bony lesions [Figure C], and significant shrinking and calcification of both the cervical and splenic lesions. She continues follow-up at the infectious disease clinic and is feeling well with a recent CD4 count of 554 cells/µl and undetectable viral load.

COMMENT

The appearance of a neck abscess in an HIV-positive patient one year after completing second-line tuberculosis therapy must prompt a meticulous workup for an infectious cause. When these investigations do not yield an etiology, one must consider a differential diagnosis of IRIS. In co-infected TB/HIV patients receiving HAART, IRIS is a common and serious cause of morbidity that can be divided into two entities. Early TB-IRIS is usually the result of underlying infection unmasked by a renewed capacity to mount an immune response. Late or paradoxical TB-IRIS is a clinical deterioration of a previously diagnosed and treated TB infection and could represent an immune response against antigens of non-viable bacteria [1]. Early TB-IRIS occurs within the first 3 months of starting HAART. Paradoxical TB-IRIS has been rarely reported beyond several months following HAART [2]. When IRIS occurs in response to a previously unrecognized pathogen, directed antimicrobial therapy should be initiated. However, when IRIS occurs in response to a pathogen for which a patient has already completed treatment, the management consists of non-steroidal anti-inflammatory drugs for mild manifestations, and steroids in the case of serious inflammation or central nervous system manifestations [1].

One lymph node biopsy, obtained 4 months after appearance of the neck abscess, stained positive on Warthin-Starry stain. Direct examination of tissue provides a presumptive diagnosis only, and definitive diagnosis requires modified bacteriological culture techniques such as inoculating blood-lysis tubes, serological and/or DNA amplification [3]. In our patient, molecular diagnosis from the same biopsy yielded no amplification product. Invasive bartonellosis including splenic and bony lesions have been described widely in AIDS patients. A case of lymph node co-infection with *Bartonella quintana and M. tuberculosis* in an HIV-infected patient with a CD4 count of 416/mm^3 demonstrated that bartonellosis does not occur exclusively in advanced immunosuppression [4]. Erythromycin is the current drug of choice for bar-

tonellosis in immunocompromised patients, although at a higher dosage (500 mg per os four times a day) than the clarithromycin received by our patient during her second TB treatment course [5]. This treatment might explain the resolution of the bony lesion if bartonellosis was the cause. Our patient's distressing lymphadenopathy, however, did not resolve until the introduction of steroids.

The prompt favorable response to steroid therapy in our patient is highly suggestive of very late TB-IRIS as the cause of the abscess, increased splenic dissemination, and lytic bone lesions. Our case underscores the importance of considering late IRIS even beyond the expected time frame after all attempts to rule active infection are exhausted. We recommend considering a treatment trial with steroids for non-resolving soft-tissue infection due to late-onset IRIS.

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References

1. French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis* 2009; 48: 101-7.
2. Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005; 19: 399-406.
3. Slater L, Welch D. Bartonella including cat-scratch disease. In: Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 7th edn. Philadelphia: Elsevier Inc., 2010: 2995-3009.
4. Bernit E, Veit V, La Scola B, et al. *Bartonella quintana and Mycobacterium tuberculosis* coinfection in an HIV-infected patient with lymphadenitis. *J Infect* 2003; 46: 244-6.
5. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother* 2004; 48: 1921-33.

Capsule

Transcranial electrical stimulation highly effective and reduced seizure duration

Deep brain electrical stimulation can be a successful therapy in Parkinson's disease, in depression, and in several other psychiatric diseases, especially in drug-resistant cases. Unfortunately, chronic, continuous stimulation is associated with multiple side effects. This could be alleviated by delivering the electrical perturbation only when it is necessary, using closed-loop stimulation. Such an approach is essential for epilepsy, where seizures occur very rarely but with serious consequences. In a rat model for epilepsy, Berényi et al. prevented seizures by transcranial electrical stimulation using a closed-loop system. Transcranial electrical stimulation was highly effective and reduced seizure duration, on average, by 60%.

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Capsule

Landscape of somatic retrotransposition in human cancers

Transposable elements (TEs) are abundant in the human genome, and some are capable of generating new insertions through RNA intermediates. In cancer, the disruption of cellular mechanisms that normally suppress TE activity may facilitate mutagenic retrotranspositions. Lee et al. performed single-nucleotide resolution analysis of TE insertions in 43 high-coverage whole-genome sequencing data sets from five cancer types. We identified 194 high-confidence somatic TE insertions, as well as thousands of polymorphic TE insertions in matched normal genomes. Somatic insertions were present in epithelial tumors but not in blood or brain cancers. Somatic L1 insertions tend to occur in genes that are commonly mutated in cancer, disrupt the expression of the target genes, and are biased toward regions of cancer-specific DNA hypomethylation, highlighting their potential impact in tumorigenesis.

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