Central Nervous System Tuberculosis Reactivation following Intravenous Iron Supplementation

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Abstract

Patients with inflammatory bowel disease (IBD) are often treated with tumor necrosis factor (TNF)-alpha inhibitors and are therefore at higher risk for tuberculosis (TB) reactivation. IBD patients also frequently have iron deficiency which is often treated with intravenous iron supplementation. Iron plays an important role in mycobacterial infections, and reactivation of TB has been rarely reported after iron repletion. We present a case of a 63-year-old male with a history of Crohn’s disease, on treatment with adalimumab for 2 years. The patient presented with malaise, mild lethargy, low-grade fever, and hyponatremia within a week after the first dose of intravenous iron. He was diagnosed with central nervous system TB (positive cerebrospinal fluid polymerase chain reaction and culture) and responded to treatment with a four-drug regimen. The timing of TB reactivation (within a week after intravenous iron administration) suggests that iron repletion contributed to the clinical reactivation of TB. Biological plausibility and prior similar clinical observations further support the causality of this association. Considering the frequency of iron deficiency in IBD, we believe that it is worthy to further explore the potential association between intravenous iron administration and the timing of TB reactivation in patients being treated with TNF-alpha inhibitors.

Keywords: Adalimumab, iron, reactivation, tuberculosis

INTRODUCTION

The relationship between nutritional status and infectious diseases is well known.[1] Iron plays an important role in mycobacterial infections.[2-5] Trousseau first described, in 1868, the deleterious effects of iron repletion on pulmonary tuberculosis (TB).[4] In 1978, Murray et al.[5] reported reactivation of preexisting malaria, brucellosis, and TB in iron-deficient Somali nomads following iron repletion. Gordeuk et al.[6] reported in 1996 (based on autopsy data of black Africans in the 1920s) that iron overload (splenic iron levels) was the variable most significantly associated with death from TB.

Treatment with tumor necrosis factor (TNF)-alpha inhibitors, such as infliximab, etanercept, and adalimumab, is another well-known risk factor for TB reactivation.[7,8] All TNF-alpha inhibitors increase the risk of TB, but the risk elevation is higher for the anti-TNF monoclonal antibodies infliximab and adalimumab compared to etanercept.[8] Most TB cases associated with TNF-alpha inhibitors are extrapulmonary (including central nervous system TB).[8]

Central nervous system TB is associated with high mortality.[9] Prompt initiation of treatment (often empirical) is important, but the diagnosis is often difficult as microbiological detection of Mycobacterium tuberculosis with acid-fast staining, culture, and even polymerase chain reaction (PCR) is insensitive.[10]

CASE REPORT

A 63-year-old male patient presented to the emergency department due to malaise and drowsiness. He reported a history of Crohn’s disease, arthritis, and anemia. Treatment with adalimumab (Humira) 40 mg every other week had been initiated 26 months before this visit and had resulted in clinical remission of both his arthritis and Crohn’s disease. He reported that his symptoms had began after his last treatment with adalimumab, 7 days before presentation, at which time...
he had also been administered 1 g of ferric carboxymaltose intravenously due to iron-deficiency anemia.

At presentation, he had an elevated blood pressure (173/90 mmHg), low-grade fever (axillary temperature 37°C), a heart rate of 97 beats per min, and a normal oxygen saturation (98%). On neurological examination, he was alert and oriented but slightly lethargic. Laboratory tests (complete blood count and chemistry panel) revealed moderate hyponatremia (127 mEq/L) and the already known microcytic anemia but were otherwise unremarkable [Table 1].

He was euvolectic clinically, the spot urine sodium was high (52 mEq/L), and serum uric acid was low (2.7 mg/dl), suggesting that syndrome of inappropriate antidiuretic hormone secretion was the mechanism of hyponatremia.

A brain computed tomography was performed which demonstrated ventricular dilation but was otherwise unremarkable. The patient was admitted for observation and further evaluation. During hospital stay, low-grade fever (up to 37.8°C) was recorded and the patient’s level of consciousness was deteriorating. A lumbar puncture was performed, and the patient was started empirically on ceftiraxone, vancomycin, ampicillin, dexamethasone, and acyclovir. Examination of the cerebrospinal fluid (CSF) revealed pleocytosis (225 cells) of lymphocytic predominance, hypoglycorrhachia (29 mg/dl), and high total protein (199.7 mg/dl). PCR for several viral/bacterial causes of central nervous system infection was performed but was negative [Table 1]. The brain magnetic resonance imaging demonstrated ventricular dilation but was otherwise normal [Figure 1].

Further medical history taking revealed that before initiation of treatment with adalimumab screening for latent TB was positive (11 mm induration on tuberculin skin testing), but the patient had not complied with the recommended treatment regimen for latent TB (he had discontinued isoniazid after only 2 months). The patient was started empirically on treatment for central nervous system TB with isoniazid, rifampicin,
pyrazinamide, ethambutol, and dexamethasone (0.4 mg/kg/day for 2 weeks followed by tapering over 8 weeks). Fever resolved within 2 days, and significant improvement in the patient’s mental status was noted. Both PCR (GeneXpert) and culture (BacT/ALERT 3D) of the CSF came back positive for *M. tuberculosis*. After 2 months with the four-drug regimen, the patient was switched to isoniazid and rifampicin. On the last follow-up, 7 months later, he remained compliant with his treatment and asymptomatic.

**Discussion**

The causality between intravenous iron supplementation and TB reactivation in our case is supported by many factors. Causality is biologically plausible[6,7] and is consistent with prior clinical observations reporting TB reactivation following iron supplementation.[8,9] Temporality in our case also supports causality. The timing of presentation of our patient, just 1 week following the first dose of intravenous iron supplementation, suggests that iron repletion contributed to the clinical reactivation of TB. Finally, a dose–response relationship is also possible. Our patient had stably low ferritin levels (ranging between 8 and 26 ng/ml) in multiple measurements during the prior 2 years, while his ferritin was 972 ng/ml a week after intravenous iron administration. Therefore, transient iron excess associated with the high-dose intravenous route of administration[10,11] may have contributed to TB reactivation. Furthermore, as already discussed, iron overload (as measured by splenic iron levels) has been previously associated with TB mortality.[12]

Treatment with adalimumab may have also contributed to TB reactivation, although our patient had been receiving this treatment for 26 months. Nevertheless, the timing of TB infection following initiation of treatment with TNF-alpha inhibitors is variable and is typically longer for adalimumab compared to infliximab.[13] Infection soon after treatment onset suggests reactivation of preexisting latent TB, while more delayed presentations may represent either new infection or delayed reactivation. Considering the positive pretreatment tuberculin skin test and the incomplete treatment for latent TB, the latter possibility is more likely. Treatment with isoniazid (even if only for 2 months) may have delayed reactivation in the case of our patient.

Considering that iron deficiency is common in inflammatory bowel disease (IBD), and that the intravenous route of iron supplementation is often preferred (due to intolerance of the oral route by IBD patients),[14] we believe that it is worthy to further explore the potential association between intravenous iron administration and TB reactivation in patients being treated with TNF-alpha inhibitors, and whether the timing of TB reactivation may be associated with the timing of intravenous iron repletion or the patients’ iron status. To our knowledge, the case presented here is the first report of such an association.

**Declaration of patient consent**

We certify that we have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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