Infection and adult T-cell lymphoma/leukaemia: a pathogenic partnership

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Abstract

Adult T-cell lymphoma/leukaemia (ATLL) is an aggressive T-cell lymphoma caused by the retrovirus HTLV-1. Its clinical presentation and course can be variable, and it may mimic other T-cell lymphomas or non-neoplastic entities. ATLL is commonly complicated by superadded *Strongyloides* infestation. In this setting, this can rapidly accelerate a patients demise, highlighting the need for awareness and vigilance of this dual diagnosis.

Keywords Adult T-cell lymphoma/leukaemia; ATLL; HTLV-1; human T-lymphotrophic virus type 1; *Strongyloides stercoralis*

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Case report

A 53 year-old female, visiting from the Caribbean, presented to the emergency department with a worsening history of diarrhoea, abdominal pain and intermittent fevers. She had also mentioned significant weight loss of over 8 kg. A stool sample which had been sent for microscopy, culture and sensitivity from her GP was negative. Her medical history was pertinent for type 2 diabetes mellitus and hypertension. She had no surgical history or recent travel history.

On examination, she was tachycardic, tachypnoeic and hypotensive. She had generalized abdominal tenderness with no specific localization. Her admission bloods demonstrated a normocytic anaemia, mild eosinophilia, lymphocytosis and an elevated corrected calcium just above normal range.

An inpatient colonoscopy revealed intermittent areas of erythema, cobblestoning, stenosis and ragged ulceration. The endoscopic impression was that of Crohn's disease/other inflammatory colitides, and biopsies were taken.

Microscopy showed mucosal ulceration and an expanded lamina propria containing a diffuse infiltration of medium-large lymphoid cells with prominent eosinophils and no discernable germinal centres (Figure 1). On higher power, the lymphoid population showed an open convoluted vesicular chromatin pattern (Figure 2). Occasional crypt abscesses were seen and cryptitis was inconspicuous. The overall architecture was distorted by the marked inflammatory infiltrate, giving the impression of patchy crypt loss and distortion. Additionally, numerous helminth forms were identified, morphologically in keeping with *Strongyloides* (Figure 3).

Immunohistochemistry highlighted the lymphoid population with pan-T-cell antigens CD2, CD3 and CD5, and showed co-expression of CD4 and CD25 (Figure 4). CD7, CD8, CD20, CD15, CD30 and ALK were negative. Cytotoxic markers Granzyme B, Perforin and TIA-1 were negative.

The suspected diagnosis of GI infiltration by a T-cell lymphoma prompted testing for Human T-cell leukaemia virus type 1 (HTLV-1); this was found to be positive.

She deteriorated acutely, requiring aggressive fluid resuscitation and inotropic support. Following a diagnosis of ATLL with

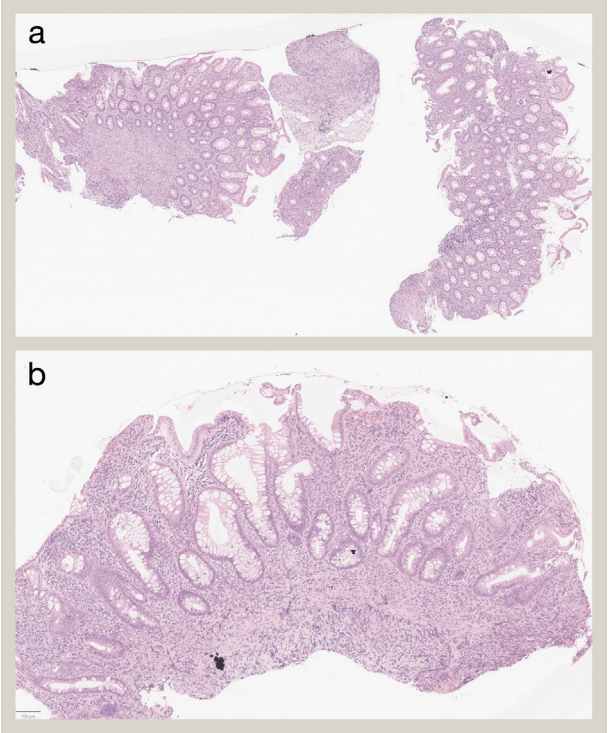

Figure 1 The (**a**) low- and (**b**) medium-power impressions suggest a possible inflammatory or infective process with no obvious dysplasia or malignancy. Active crypt injury is inconspicuous. There is patchy ulceration and crypt distortion secondary to a lymphoid infiltrate within the lamina propria.

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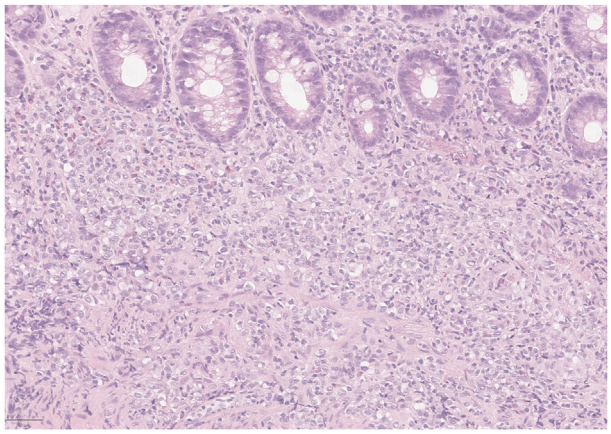

Figure 2 The lymphoid infiltrate is clearly abnormal here; it is comprised of a diffuse infiltrate of large atypical lymphoid cells with convoluted vesicular nuclei. The background is polymorphous and contains abundant eosinophils.

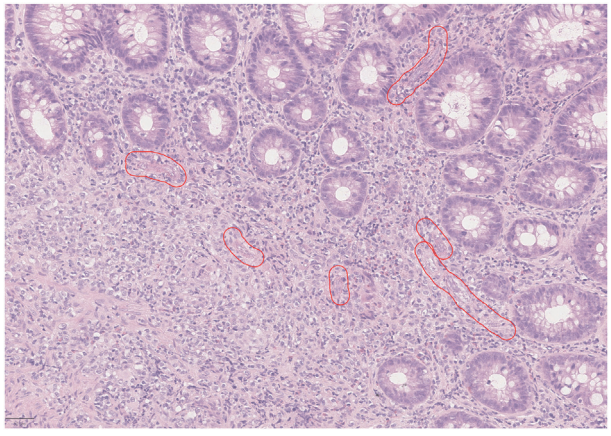

Figure 3 *Strongyloides* infestation: numerous adult nematodes are outlined within the lamina propria and are intermixed within the lymphomatous infiltrate. Adult worms were also present within crypt lumens. Eosinophils are the usual inflammatory cell associated with parasitic infections.

superadded strongyloidiasis, she was commenced on chemotherapy and anti-helminth treatment.

Discussion

HTLV-1 was the first pathogenic human retrovirus to be discovered and is the causative agent of ATLL and HTLV-1-associated myelopathy (also known as tropical spastic paraparesis). It is estimated to infect 4–10 million people worldwide per annum through direct contact with infected bodily fluids including blood, breast milk and semen. The retrovirus is endemic to the Caribbean basin, South America, Western Africa and southwestern Japan. In the vast majority of cases, HTLV-1 infection remains asymptomatic. A small proportion (around 5%) develop a chronic persistent infection within CD4 + regulatory T-cells, which can develop into the aggressive and lethal ATLL with a latency period counted in the order of decades.[1]

Our current understanding of HLTV-1's oncogenic abilities involves a multi-hit model:[2] the HTLV-1 genome encodes two proteins, Tax and HBZ which act as key early initiators in

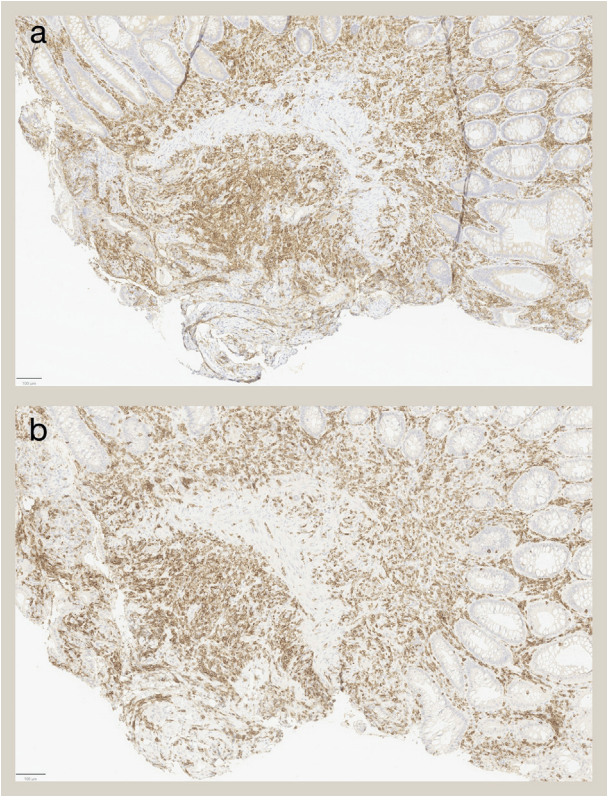

Figure 4 ATLL does not adopt a specific immunohistochemical staining pattern, although most cases show positive staining for antibodies (**a**) CD25 and (**b**) CD4. A negative CD4 should not dissuade one from making the diagnosis. Tumour cells tend to express pan-T-cell antigens CD2, CD3 and CD5 and generally lack CD7.

promoting T-cell activation, expansion, and survival. There are subsequent genetic and epigenetic aberrations including mutations in TP53 and T-cell receptor NfkB-related genes, which when compounded, provide sufficient genetic instability to promote carcinogenesis. Evasion of immunosurveillance also appears integral to the viruses pathogenic behaviour; ATLL cells demonstrate marked DNA promoter hypermethylation with subsequent transcriptional silencing in genes specific for immune recognition, in particular MHC-1. Likewise, ATLL cases with mutated HLA-A and HLA-B demonstrate a poorer prognosis.[3]

ATLL manifests as four clinical subtypes: acute, lymphomatous, chronic and smouldering; defined by the pattern of organ involvement, with the more aggressive subtypes (acute and lymphomatous) representing the majority of cases. As such, the clinical presentation is variable and non-specific and may include widespread lymphadenopathy, hepatosplenomegaly and features secondary to direct organ infiltration, particularly the CNS, GI tract, bone and lung, or a combination thereof. Cutaneous infiltration is present in around half of ATLL patients and represents the commonest extranodal site of involvement; the lesions are polymorphous and may be clinically indistinguishable from other leukaemic infiltrations. Interestingly, skin lesions are less common in patients with GI infiltration by ATLL.[4]

Laboratory investigations often reveal a lymphocytosis, elevated serum LDH and a paraneoplastic neutrophilia/esosinophilia. Histologically, ATLL is well known to mimic almost any type of T-cell lymphoma or leukaemia. In our case, the striking

colonic lamina propria infiltration may at first bring into question a particularly florid case of inflammatory bowel disease. This is made more challenging by the endoscopic appearances which can closely match this and may contribute towards an unwitting confirmation bias. The large atypical lymphoid cells and marked nuclear pleomorphism seen on higher power is incompatible with an inflammatory process and should trigger a high index of suspicion for a lymphomatous infiltration instead.

Neoplastic ATLL cells show a range of morphologies depending on the clinical subtype they adopt; the more aggressive acute and lymphomatous forms typically demonstrate large cells with coarse chromatin and prominent cerebriform nuclear lobulation, reminiscent of a flower petal. These cells may also be detected in peripheral blood films. The cells of the chronic and smouldering forms may be smaller and show less marked atypia. A T-cell panel tends to show retention of pan-T cell markers CD2, CD3 and CD5. CD25 is positive in most cases and may be a useful clue to the diagnosis. CD7 is usually lost. Most cases are CD4 + CD8-, but variations in this should not deter one from making a diagnosis of ATLL, as other combinations including double positive and double negative are recognized. The polymorphous inflammatory background rich in eosinophils may render differentials such as angioimmunoblastic T-cell lymphoma and Classical Hodgkin lymphoma worth considering, however the crucial and essential distinguishing feature in ATLL is detection of HTLV-1 antibody or demonstration of monoclonal proviral HTLV-1 DNA integration.

Strongyloides stercoralis is a parasitic nematode and is the major causative agent of strongyloidiasis in humans. In immunocompetent patients, the disease may be entirely asymptomatic or produce minor non-specific symptoms. Pruritis is a common initial symptom as it represents cutaneous penetration by the filariform (infective stage) larvae. The helminth becomes of utmost significance in the context of immunocompromise, as autoinfection and systemic dissemination carries a high mortality rate of up to 80%.[5] Interestingly, a negative travel history doesn't necessarily rule out the disease[6] and microscopic examination of single stool samples has a poor sensitivity. Enzyme immunoassays can be utilized in instances where there is a high index of suspicion and repeated stool examinations have not identified the rhabditiform larvae.[7]

In view of the often vague clinical presentation, best practice guidance focuses on early detection and maintaining a high index of suspicion in at risk patients. A large study comprising over 5000 patients showed a 5.2% prevalence of *S. stercoralis* co-infection in HTLV-1 positive patients.[8] Salles'[9] team have suggested that helminthic infection has a modulatory role in HTLV-1 oncogenesis and that *S. stercoralis* co-infection may be a cofactor in the development of ATLL.

The characteristic biopsy finding is the presence of all stages (larvae to filariform) of the worm embedded in mucosal crypts, within granulation tissue or inside lymphatic spaces. This may be accompanied by a mixed inflammatory infiltrate composed of lymphocytes, plasma cells and prominent eosinophils. Typically the small intestine is most affected, but as with our case, colonic involvement is also possible.

Conclusion

This report describes a de novo presentation of ATLL manifesting within the GI tract with concurrent *Strongyloides* infection. It is imperative to keep an open mind at the time of initial slide review and not to allow biases from the endoscopic or clinical impression skew ones interpretation unduly – including the possibility of a double diagnosis. This is critical to identify in this case, in view of the high rate of mortality associated with disseminated strongyloidiasis. A T-cell lymphoma workup should raise the question of the patient's HLTV-1 status. ◆

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Practice points

- HTLV-1 is an obligate infection in the pathogenesis of ATLL. A comprehensive T-cell lymphoma workup should include HTLV-1 testing
- Strongyloidiasis is a serious opportunistic infection in immunocompromised patients and there is a well recognized association between ATLL and *Strongyloides* infestation. Its symptoms are often non-specific and may be masked by the underlying lymphoma. A high index of suspicion and close scrutiny of biopsies obtained from the GI tract is prudent

Self assessment multiple choice questions

1. The commonest site of extranodal involvement in ATLL is?

- **A. Mediastinum**
- **B. Bone**
- **C. CNS**
- **D. GI tract**
- **E. Skin**

Correct answer: E

2. Which of the following statements is true about ATLL?

- **A. CD4 and CD25 positive staining is specific for this diagnosis.**
- **B. HTLV-1 antibody detection is confirmatory.**
- **C. Usually has normal blood counts and a normal peripheral blood film.**
- **D. Loss of CD2, CD3, CD4 and CD8 is common.**

Correct answer: B

3. In what stage(s) of development may *S. stercoralis* organisms be identified in biopsies?

- **A. Larval form (rhabditiform)**
- **B. Infective form (filariform)**
- **C. All life cycle stages**
- **D. Adults only**
- **E. Eggs and larval rhabditiforms**

Correct answer: C