CASE REPORT

Misdiagnosing Whipple's disease in the young

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SUMMARY

Whipple's disease is considered an infection of middle-aged white men of European ancestry. Cases are rare and disproportionately associated with occupational exposure to soil or animals. We report the case of a man aged 22 years with no risk factors, erroneously diagnosed with, and treated for, toxoplasmosis on the basis of consistent lymph node histology. The correct diagnosis was delayed by the dramatic symptomatic improvement resulting from this therapy. Whipple's disease should be considered in cases of granulomatous lymphadenopathy of unknown cause, even if the age of the patient does not fit the classic presentation of the disease.

BACKGROUND

Whipple's disease is a rare systemic infection with an estimated incidence in the general population of 3/1 000 000.¹ The causative agent, the bacterium *Tropheryma whipplei*, is ubiquitous in the environment—and indeed, there is evidence that it is a cause of childhood diarrhoea. It is considered an infection of middle-aged men of European origin, presenting with chronic symptoms of joint pain, diarrhoea and malabsorption.² However, the spectrum of disease is wide and diagnosis is often delayed.³ In this paper, we present the case of a young man, without risk factors, who presented to us with a variety of non-specific symptoms and signs, initially misdiagnosed and treated as presumed toxoplasmosis.

CASE PRESENTATION

A man aged 22 years was referred to the infectious disease service from a haematologist based at another institution. He had been unwell for over

3 months with lethargy, sweats, fever, weight loss of 12 kg and cervical lymphadenopathy. Anaemia (haemoglobin 11 g/L (133–166)) had been noted and a CT thorax and abdomen revealed multiple peripancreatic, periportal, perigastric, aortocaval and mesenteric nodes. Lymph node biopsy from the neck demonstrated microgranulomata without necrosis which were interpreted as suggestive of toxoplasmosis (figure 1).

Prior to this illness, he had been fit and well and was studying for a degree in electrical engineering. He did not use recreational drugs, had no pets and had travelled in the previous year to the Balearic Islands and Lithuania. On examination, small, rubbery inguinal lymph nodes were palpable. There were no other abnormalities.

Blood tests demonstrated neutrophilia of $11.1 \times 10^9/L$ (2–7.5), C reactive protein (CRP) 63 mg/L (0–5), alkaline phosphatase 263 IU/L (30–130) and alanine aminotransferase (ALT) 97 IU/L (0–55). As toxoplasma IgG was negative, a second histopathological opinion was sought. After review, it was felt that these microgranulomata were consistent with toxoplasmosis, despite the negative IgG, a phenomenon that had been encountered previously by the reporting pathologist.^{4–6}

He returned for clinical review 3 weeks later. Liver enzymes and inflammatory markers had improved somewhat, and he was feeling better. On further review a month later, his liver enzymes remained abnormal and he was provided with a month's treatment of clindamycin and pyrimethamine. He made a full recovery and gained weight over the next few months.

After 5 months, he developed a purpuric rash. This was biopsied at his local hospital and he was given a diagnosis of Henoch-Schönlein purpura. The rash resolved spontaneously and he remained well for the next 9 months after which his symptoms returned. He developed extreme fatigue, drenching night sweats, fevers of up to 39°C, rigours and 5 kg weight loss, and was referred back to the infectious disease service. No other abnormalities were detected on examination. There had been no further travel or any other changes in his circumstances.

INVESTIGATIONS

On reattendance to the infectious diseases clinic, he was found to have peripheral leucocytosis with neutrophils of $12.0 \times 10^9/L$ (2–7.5), CRP of 124 mg/L (0–5) and moderated liver dysfunction with an ALT of 90 IU/L (0–55). His ferritin level was raised (1000 ng/mL) and he had a folate deficiency with plasma folate of 2.4 µg/L (3.1–20.5).

Figure 1 Histology of the lymph node (cervical node) shows two microgranulomas (arrow) at the edge of a germinal centre. H&E x200. Inset shows Periodic acid-Schiff (PAS)-positive macrophages. PAS x400.

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Figure 2 The lamina propria of the duodenal mucosa is infiltrated by a sheet-like proliferation of macrophages with abundant foamy cytoplasm. H&E $\times 200$. Inset. The macrophages contain abundant Periodic acid-Schiff (PAS)-positive material. PAS $\times 400$.

The CT was repeated revealing moderately bulky lymphadenopathy in the upper abdomen, small bowel mesentery and para-aortic region. The spleen was enlarged and there was mild hepatomegaly. Repeat toxoplasma, syphilis, HIV, Cytomegalovirus, Epstein-Barr virus and hepatitis serological tests were all negative, as were antinuclear antibody, antineutrophil cytoplasmic antibodies and blood cultures.

The patient referred for an oesophagoduodenoscopy (OGD) with duodenal biopsy and a CT-guided para-aortic lymph node biopsy. Histology of the duodenal mucosa showed focal expansion of the lamina propria by a proliferation of Periodic acid-Schiff (PAS)-positive macrophages (figure 2). Few small foci of PAS-positive foamy macrophages were present in the para-aortic lymph node and on review of the initial lymph node. These specimens subsequently tested positive for *Tropheryma whipplei* on PCR.

DIFFERENTIAL DIAGNOSIS

Given the clinical presentation and radiological and histological findings, the initial differential was broad and included a variety of illnesses, which could cause similar presentation and granulomatous lymphadenitis. We investigated for infectious causes such as mycobacterial infections, toxoplasmosis, viral hepatitis, HIV and Whipple's disease, and non-infective conditions such as vasculitis and lymphoproliferative diseases. Since Whipple's disease is a rare systemic illness, more common conditions such as lymphoma needed to be excluded first.

TREATMENT

He was treated with intravenous ceftriaxone and after 1 month, he was switched to oral cotrimoxazole with a planned duration of 12 months.

OUTCOME AND FOLLOW-UP

He made a prompt response with significant weight gain and cessation of fevers. Treatment monitoring will continue with an OGD and repeat duodenal biopsies before stopping treatment.

DISCUSSION

Whipple's disease is caused by infection with *T. whipplei*. The organism is difficult to culture, thus the diagnosis is generally made on the basis of duodenal histology. The presence of

PAS-positive macrophages filled with bacilli, infiltrating the lamina propria of the small intestine is characteristic but not pathognomonic⁷ and such findings may occur in association with other infections, for example, *Mycobacterium avium intracellulare*, *Rhodococcus equi* or some parasitic and fungal diseases.^{8 9}

The patient described was initially diagnosed with toxoplasmosis, despite negative toxoplasma IgG, on the basis of histological findings on lymph node biopsy. The biopsy demonstrated small microgranulomata without associated necrosis closely associated with lymphoid follicles, findings which are consistent with evidence-based criteria for the histological diagnosis of toxoplasmosis.⁴ The histological examination was verified by three experienced histopathologists and the patient initially responded to treatment targeted at toxoplasmosis. The diagnosis of Whipple's disease was suggested after symptom relapse and confirmed by the findings of a duodenal biopsy and positive PCR identification of the organism. The initial response to treatment was attributed to the fact that *T. whipplei* has in vitro sensitivity to erythromycin and is therefore likely to be clindamycin-susceptible (both drugs inhibit RNA-dependent protein synthesis by the same mechanism).¹⁰

Granulomatous lymphadenopathy is a rare feature of Whipple's disease and described in individual case reports in which the diagnosis is confirmed by PCR.¹¹ In this case, Whipple's disease was not suspected at first presentation and PCR was not performed. Retrospective PAS staining of the cervical lymph node did show subtle changes consistent with Whipple's disease. These were not diffuse and given the patient's age (22 years at the time of symptom onset) and non-typical symptoms, it is not surprising the changes were attributed to toxoplasmosis. To the best of our knowledge, only two cases of younger adult have been reported worldwide.¹²

Learning points

- ▶ Whipple's disease is a rare cause of granulomatous lymphadenopathy, but it should be considered in those with systemic features in which no other cause is identified.
- ▶ Periodic acid-Schiff staining should be considered in granulomatous biopsies without obvious explanation.
- ▶ While the peak of incidence is in those of middle age, it is by no means restricted to this group.

Contributors EM, DP and MR provided clinical care for the patient. GL performed the histological examination and provided the relevant histological pictures for the paper. DP and MR wrote the manuscript and contributed equally to this report. EM supervised the case throughout and corrected the manuscript. GL also corrected the article. All authors have seen and approved the manuscript and have contributed significantly to the work.

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