GASTRO-INTESTINAL *MYCOBACTERIUM AVIUM* COMPLEX AS A CAUSE OF ANAEMIA

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Anaemia is a relatively common finding in HIV-positive patients, with rates (among females) as high as 37%, compared with their HIV-negative counterparts (17%). Anaemia of chronic disease plays a very important role in this population group, and is estimated to occur in 18 - 95% of cases. For this reason, it is imperative to distinguish this condition from other underlying or concurrent causes of anaemia that may warrant treatment. This clinical case illustrates the value of critically evaluating the parameters of a full blood count and haematinic screen, to so determine which patients warrant further workup.

CASE REPORT

A 43-year-old man, known to be HIV-1 positive, presented to the casualty department at Kalafong complaining of a 2-week history of fatigue, weight loss, night sweats, dysphagia and general malaise. He further described a 3-day history of vomiting and diarrhoea, with no melaena or haematemesis.

At the time of presentation, he had been on first-line highly active antiretroviral (HAART) therapy for 2 years. Despite this the CD4 count on admission was 3 cells/µl. In the light of this finding, non-compliance was suspected. He had previously been diagnosed with

disseminated *Mycobacterium avium-intracellulare* by positive blood cultures and had been started on treatment. Owing to side-effects, he had not complied with this treatment regimen either.

On admission he was pyrexial and tachycardic. He was clinically anaemic with no signs of oral hairy leukoplakia or candida. Although abdominal examination was unremarkable (with no hepatomegaly or splenomegaly), he was tender in the epigastric area. Cardiovascular and respiratory examinations were essentially normal.

The full blood count revealed a significant microcytic hypochromic anaemia (haemoglobin 5.8 g/dl, mean corpuscular volume 68 fl and mean corpuscular haemoglobin 20.4 pg). The white cell count was normal, but he had thrombocytopenia (30×10^9/l). Creatinine and electrolyte levels were normal. Liver function tests revealed an isolated mildly raised gamma-glutamyl transpeptidase (GGT) level (70 U/l) and a low albumin level (16 g/l). C-reactive protein was elevated at 84.9 mg/l. Iron studies were also performed and showed low serum iron (1.3 µmol/l) and transferrin (1.4 g/l) levels and transferrin saturation (4%), and a markedly elevated serum ferritin level (1 579 µg/l).

As part of the work-up for anaemia, the upper gastro-intestinal tract was investigated by endoscopy. This revealed what was clinically judged to be extensive candidiasis throughout the oesophagus. The stomach was normal but the duodenum also had extensively distributed white plaques. A biopsy specimen of these plaques was taken and submitted for histological examination. An H&E stain was performed (Fig. 1, a). The periodic acid-Schiff (PAS) stain revealed multiple clusters of micro-organisms in the histiocytes (Fig. 1, b). Finally, a Ziehl-Neelsen (ZN) stain was performed, showing large numbers of acid-fast bacilli (Fig. 1, c and d). A diagnosis of disseminated *M. avium* complex (MAC) was suggested, as the organisms were found intracellularly. The diagnosis of disseminated MAC was confirmed on a urine sample by molecular techniques.

DISCUSSION

Patients with advanced HIV-1 disease pose a multitude of challenges in terms of diagnosis and treatment. Anaemia is a relatively common finding in HIV-positive patients, with rates (among females) as high as 37%, compared with their HIV-negative counterparts (17%).[1] The list of possible causes of anaemia in HIV-positive patients is substantial and differentiation is often difficult. Value is certainly added by taking the full blood count results into consideration. A simple distinction between red cell size (reflected in mean corpuscular volume) and red cell haemoglobin content (reflected by mean corpuscular haemoglobin) can significantly contribute to further choices in testing.

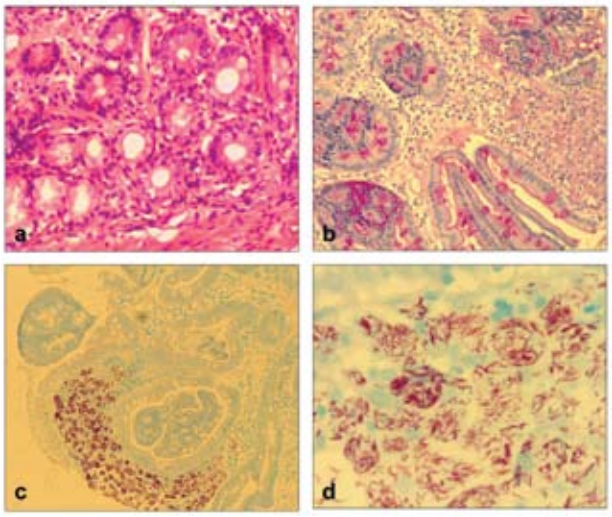

Fig. 1. Sections from white plaques biopsied in duodenum: a – H&E stain; b – PAS stain showing numerous clumps of organisms in histiocytes; c – ZN stain showing clumps of acid-fast bacilli; d – closer view of collection of acid-fast bacilli in ZN stain.

Anaemia of chronic disease plays a very important role in this population group, as inhibition of iron transfer from the reticulo-endothelial cells to the erythroid precursors due to inflammation is estimated to occur in 18 - 95% of cases.[2] For this reason, it is imperative to distinguish this condition from other underlying or concurrent causes of anaemia that may warrant treatment. A haemoglobin level below 8 g/dl should prompt further investigation, as anaemia of chronic disease rarely causes World Health Organization grade III or IV anaemia[2] (grade III <7.9 g/dl, grade IV <6.5 g/dl).[1] Iron studies may facilitate this process. In both iron deficiency anaemia and anaemia of chronic disease, the serum iron level and transferrin saturation will be reduced. The transferrin level, however, may facilitate in making a distinction as it is typically reduced to normal in anaemia of chronic disease and increased in iron deficiency. A further indicator can be found in serum ferritin levels, which are reduced to below 30 ng/l (positive predictive value of 92 - 98%) in iron deficiency, and normal to elevated in anaemia of chronic disease. The inherent confounder with using ferritin is the fact that it acts as an acute-phase reactant and will be elevated beyond its baseline in any inflammatory condition, irrespective of iron status.[2]

The soluble transferrin receptor level may be a useful assay to delineate causes of anaemia. Levels are typically increased in iron deficiency and essentially normal in anaemia of chronic disease, as inflammatory cytokines negatively influence its expression. This can also be very useful if co-existence of both conditions is suspected. However, the assay is not universally offered. The use of various ratios has also been proposed as possibly helpful in determining the underlying cause of anaemia.[2]

The finding and confirmation of iron deficiency should prompt further investigation as to the underlying cause.

Imaging of the gastro-intestinal tract may be useful, especially if clinical features are suggestive. Of note is the fact that the only feature suggestive of upper gastro-intestinal bleeding in our patient was the epigastric tenderness on abdominal examination. It is therefore prudent to have a high index of suspicion. Again, the differential diagnosis in this clinical setting is large and relates to the degree of immunosuppression.[3]

Disseminated MAC is the most common bacterial opportunistic infection among HIV-1-positive patients in the First World.[4] However, it appears to be less common in our local setting.[5] It has been postulated that it is caused by the overwhelming presence of *M. tuberculosis* in the South African context.[5] Patients with a CD4 count below 50 cells/µl and possibly high HIV-1 viral loads are at increased risk of MAC infections, which have been shown to be an independent predictor of mortality. For this reason prophylaxis is advocated by some.[4] It is, however, not included in the current South African *National Antiretroviral Treatment Guidelines.*[6]

MAC can affect any part of the gastro-intestinal tract, with the duodenum being the most common site. Macroscopic findings are not diagnostic. Biopsy and culture is therefore the mainstay of diagnosis of this condition.[3]

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Invited Comment

Abdominal mycobacterial infection in HIV

The articles in this edition by Kao and Hung and Van de Vyver and Visser both deal with aspects of abdominal mycobacterial infections. Van de Vyver's article highlights the importance of investigating abnormalities that cannot be attributed to HIV infection alone, and demonstrates that abdominal mycobacterial infection may present with a paucity of abdominal symptoms and signs. While tuberculosis (TB) infection is predominant in South Africa, non-tuberculous mycobacteria should always be considered in patients with advanced immunosuppression. The article by Kao demonstrates a more dramatic presentation in a patient with relatively preserved immunity. Notification rates of extrapulmonary TB in South Africa are increasing, and it is likely that more patients will present with abdominal tuberculosis.[1] Tuberculosis can involve the entire gastro-intestinal tract, from the intra-abdominal organs to the peritoneum. The spectrum of symptoms seen in abdominal TB range from insidious nonspecific complaints that may be mistaken for the constitutional symptoms of HIV infection, to an acute abdomen.[2] With improved access to antiretrovirals, TB immune reconstitution inflammatory syndrome is being seen more frequently and often involves the abdomen.[3]

In resource-limited facilities, investigations such as abdominal computed tomography scanning and laparoscopic peritoneal biopsy are seldom available. However, abdominal ultrasound, specifically looking for hepatomegaly, ascites, splenic micro-abscesses and intra-abdominal lymphadenopathy, is a useful investigation for assessing HIV-infected patients with suspected abdominal tuberculosis.[4]

Clinicians need to maintain a high index of suspicion for TB in patients with HIV and abdominal symptoms. In the correct clinical setting empiric anti-tuberculosis therapy is warranted. All patients started on anti-tuberculosis therapy need close follow-up until resolution, and those who fail to respond to TB therapy may require further investigation. Non-tuberculosis mycobacterial infection should be considered in patients with advanced immune deficiency.

While abdominal tuberculosis in HIV-infected patients is best managed with standard TB therapy and anti-retrovirals, complications such as obstruction, perforation and large abscess formation may require surgical intervention.[2] Depending on clinical presentation, early consultation with the surgeons is essential and if required surgery should not be delayed.

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