Infectious mononucleosis: not always what it seems

Infectious mononucleosis (IM) is a benign disease of healthy young people. Patients and their relatives therefore expect a speedy and complete recovery. This editorial explores some of the unexpected diagnostic and management problems encountered in this otherwise commonplace illness.

INTRODUCTION

'Glandular fever' is a catch-all diagnosis which embraces a number of diverse acute infections, all of them characterized by lymphoproliferation. In some cases (Epstein–Barr virus, EBV; human immunodeficiency virus, HIV) the causative agent specifically targets lymphocytes, while in others (cytomegalovirus, toxoplasmosis) there is a much wider range of host cells and tissues infected. In all cases, however, infection provokes a cellular immune response which contributes to the lymphoproliferation.

EBV-induced IM is by far the commonest form of glandular fever, and has a reputation as a benign self-limiting illness affecting previously healthy young people. However, the other microbial causes of the syndrome may have much more serious consequences, and IM itself can lead to severe or prolonged illness, or occasionally prove fatal.

NOT ALWAYS EBV INFECTION

The quickest and most convenient way of confirming a diagnosis of IM is to use a heterophile antibody test such as the Mono test (Meridian Diagnostics Inc, Milan, Italy). The presence of heterophile antibody is very specific for IM and occurs in 85–90% of young adults with this infection. It is sensible to repeat an initially negative test.

Heterophile-negative illness should prompt a request for specific EBV serology to confirm or exclude acute infection with this virus, and should raise the possibility of alternative diagnoses. Acute HIV infection produces a clinical picture very similar to IM, and should be considered in anyone at risk (Kahn and Walker, 1998). Symptoms and signs include fever, fatigue, rash, lymphadenopathy, pharyngitis, and myalgia or arthralgia. About half of all patients with this HIV 'seroconversion illness' have gastrointestinal symptoms including diarrhoea.

Laboratory test results, such as thrombocytopenia or raised transaminase levels, may also misleadingly suggest a diagnosis of IM, although atypical lymphocytosis is uncommon. A diagnosis of acute HIV infection should not be overlooked. Apart from other considerations, early antiretroviral therapy may promote long-term suppression of viraemia and slow down disease progression. Further evaluation is needed to confirm this observation.

HIV antibody tests are usually negative in patients presenting with symptoms of acute infection. Diagnosis is more reliably established by blood tests to detect HIV p24 antigen or RNA (using the polymerase chain reaction) and by a follow-up HIV antibody test 6–12 weeks later to confirm seroconversion.

Heterophile-negative illness in other situations also merits further investigation. During pregnancy particular care should be taken to exclude HIV seroconversion and other infections which are potentially damaging to the fetus. There is no evidence that EBV-related IM is dangerous in pregnancy. However, cytomegalovirus infection, rubella and toxoplasmosis can all mimic IM and pose a definite threat to the fetus. Diagnosis of these infections is essentially serological and close liaison with the laboratory is recommended.

NOT ALWAYS 'CLASSICAL'

EBV-related IM is relatively easy to diagnose in adolescents and young adults who present with classical symptoms, i.e. fever, pharyngitis, tonsillar exudate, lymphadenopathy and splenomegaly. Outside the usual age range the clinical features are often less specific. In children under 10 years of age the illness is mild and short-lived, while in adults over 30 years of age it can be severe and prolonged. In both groups pharyngeal symptoms are often absent.

Diagnostic problems may also occur when IM presents with jaundice, a fever of unknown origin, or with neurological involvement, e.g. meningoencephalitis or a cranial nerve palsy. Absence of the classical atypical lymphocytosis may cause further diagnostic confusion.

NOT ALWAYS BENIGN

Serious complications of IM are fortunately uncommon but may be severe or even life threatening.

Auto-immune haemolytic anaemia presents 1–8 weeks after the onset of illness, and affects between 0.5 and 3% of individuals with IM. Most patients are jaundiced and 75% have splenomegaly. Haemolysis is usually mediated by immunoglobulin M cold agglutinins directed against the i antigen of human red blood cells. Anti-i titres return to normal 2–3 months after onset, with resolution of the haemolysis. Corticosteroid therapy, which is of uncertain effectiveness, is best reserved for patients with severe anaemia.

Although lowered platelet counts are common in IM, severe thrombocytopenia and bleeding are rarely encountered. Peripheral destruction of platelets may be responsible for the thrombocytopenia, which often

responds to corticosteroid therapy. Splenectomy is rarely necessary.

Neurological disorders occur in less than 1% of patients admitted to hospital. The commonest manifestations are meningoencephalitis and cerebellitis; polyneuritis, cranial nerve palsies, and transverse myelitis are also described. Since the heterophile antibody test may be negative the differential diagnosis is wide and will include the neurological complications of HIV infection. Management of these complications is supportive and the role of corticosteroids is uncertain. Around 85% of patients will make a complete recovery.

Death from IM is rare: the most frequent causes among previously healthy people are neurological complications, splenic rupture (Asgan and Begos, 1997), and upper airways obstruction (Boglioli and Taff, 1998).

Rupture of the spleen should be suspected in anyone with IM who complains of abdominal pain, as this symptom is otherwise uncommon. The rupture may be spontaneous, or follow minor trauma, and may be the presenting feature of IM. The onset may trigger a neutrophil response which obscures the usual lymphocytosis. Conservative management may occasionally be indicated, e.g. with a subcapsular splenic haematoma, but in most cases splenectomy will be necessary.

Upper airways obstruction from oedema and tonsillar enlargement often responds to corticosteroids, but if life-threatening will require treatment by intubation and tracheostomy. Very rarely, acute EBV infection in healthy people can be overwhelming and cause death by massive infection in many organ systems. Progressive fatal disease also affects rare individuals who inherit a specific EBV-related immune defect. In this condition (Duncan syndrome — X-linked lymphoproliferative disease) acute EBV infection in young males leads to death from multi-organ failure. Cytotoxic T cell and natural killer cell activity appears to be directed not towards EBV-infected lymphocytes, but against the cells of normal organs and tissues.

NOT ALWAYS SHORT LIVED

Prolonged recovery after IM is part of the medical folklore. Recently, however, it has become clear that some 9% of patients with IM and other glandular fever illnesses will develop a well-defined fatigue syndrome which persists for longer than 6 months after the onset of illness (White et al, 1998). Other acute infections are not associated with such a high incidence of fatigue, and so the association appears to be specific. Although latent infection with EBV always becomes established after IM, there is very little evidence that chronic fatigue is associated with increased or abnormal viral replication.

The association between glandular fever and chronic fatigue therefore remains problematic. It is possible that the explanation lies less with the virus and more with the host: in adolescents and young adults, personal, educational and social stresses may act as additional precipitating factors. Treatment for established chronic fatigue syndromes is now evidence based: the majority of patients will respond to a programme of graded exercise especially when it is combined with careful explanation of symptoms (Powell et al, 2001).

CONCLUSION

IM is a familiar illness of young people, usually best known for its association with kissing and its undesirable effects on examination results. It is nevertheless worth remembering that other illnesses including HIV infection may mimic the disease, and that even classical IM may have severe or long-lasting consequences for the patient's health. HM

KEY POINTS

- The heterophile antibody test is highly specific for infectious mononucleosis (IM), and in young adults has a sensitivity of 85–90%.
- Heterophile-negative illness raises the possibility of pathogens other than Epstein–Barr virus.
- Acute human immunodeficiency virus infection may closely mimic IM, and should be considered in anyone at risk.
- Other causes of heterophile-negative illness include rubella, cytomegalovirus and toxoplasmosis. All are potentially dangerous in pregnancy.
- IM may present atypically, particularly outside the usual age range.
- IM may be complicated by haemolytic anaemia, thrombocytopenia, and acute neurological syndromes such as encephalitis or neuritis.
- Rare life-threatening complications include severe airways obstruction, ruptured spleen, and overwhelming Epstein–Barr virus infection.
- About 9% of IM patients will develop a disabling chronic fatigue syndrome.

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