INFECTION AND IMMUNITY

Entry for

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Introduction

The interaction between man and microorganism is complex. The spectrum of disease that results when a microbe gains access to the human body ranges from asymptomatic infection to fulminating disease. Central to this interaction are two factors: the virulence of the microorganism, and the competence of the host defences. The most virulent infections can cause severe, if not fatal illness, although active intervention by the clinician may modify the outcome. However the host defences will overcome the majority of infections. These defences comprise the two arms of immunity: the specific and non-specific defences. The complement cascade and phagocytic cells comprise the non-specific elements, often of importance in the early stages of infection. Humoral and cell mediated immunity, the specific elements directed against a given microorganism, take several days before reaching their full effectiveness and so tend to play a greater role in the later stages of infection.

The six cases presented here illustrate various aspects of infection and immunity. The first, a viral infection for which there is no specific treatment, represents the natural history of many infections. Invasion of the host tissues occurs, damage being caused partly by a direct cytopathic effect of the virus, but also by non-specific damage mediated by the immune response. The second case is an infection by a highly virulent organism. Without treatment this infection would be fatal. However given early diagnosis and treatment, a complete recovery might be expected. Organisms of low virulence do not cause disease unless the host defences are compromised, so allowing invasion to occur. The third case illustrates this. The next case is another infection by an organism that favours the compromised host. Untreated it has a high mortality; with direct intervention medical treatment can alter this outcome. The final two cases are examples of autoimmunity. Although the immune system plays a critical role in combatting infection, occasionally it is directed against the host and disease results. Two different infections are seen to initiate this process, pathology resulting in different organs.
Hepatic Encephalopathy

A twenty-five-year-old male delicatessen owner was admitted with jaundice. He had been well until six days previously when he developed nausea, a cough productive of purulent sputum and vague upper abdominal pain. Normally a heavy smoker he developed a distaste for cigarettes, two days later became constipated and noted his urine to be darker than normal. He stayed in bed for the next few days complaining of anorexia, nausea and tiredness. Finally he called his General Practitioner who observed that he was jaundiced and admitted him to the Infectious Diseases unit.

On questioning he denied intravenous drug abuse, said he had never received blood products, was not homosexual and had no recent history of travel abroad. His girlfriend had never had hepatitis, he took no medication and drank only moderate amounts of alcohol. Three months previously he had been investigated for a possible Grand Mal seizure, however all investigations including an electroencephalogram and computerised axial tomography had been normal. At this time his liver function tests were normal. Both his parents had had tuberculosis, his mother dying from the disease. The remainder of his history was unremarkable.

On examination he was quite deeply jaundiced but had none of the cutaneous stigmata of chronic liver disease. Although occasionally muddled in his speech he was correctly orientated for time and place. There was no evidence of asterixis nor foetor hepaticus. A tender liver edge was palpable three centimetres below the costal margin, however there was no splenomegaly or lymphadenopathy and he was afebrile. Dipstick urine analysis demonstrated the presence of moderate amounts of bilirubin but no urobilinogen. Liver function tests were performed: his bilirubin was raised at 126 μmol/l, his alanine transaminase massively increased at 4500 u/l with lesser rises in alkaline phosphatase and gamma-glutamyl transferase (210 u/l and 143 u/l respectively).
The total protein and albumin were normal, the blood urea at the lower limit of normal (2.5 mmol/l), but, significantly, his prothrombin ratio was lengthened at 1.5.
The history and the results of these investigations were suggestive of an acute viral hepatitis, which was confirmed when serology tests showed that he was HBsAg positive, but anti-HBcAg and anti-HBsAg negative. The diagnosis then was acute hepatitis B (HBV) infection.

There being no specific treatment, he was managed conservatively with bed rest and a good diet. However, over the next few days, his jaundice deepened and his condition worsened with an element of encephalopathy supervening.

He was less alert, with poor concentration, at times appearing confused. In addition, constructional apraxia, a sensitive assay of encephalopathy, could be demonstrated (Figure 1). His bilirubin and transaminase levels continued to rise and the prothrombin time lengthened (Table 1). His condition was now giving rise to considerable concern and supportive measures were started to minimise the effects of the hepatic dysfunction.

To reduce the production of toxic compounds, such as ammonia, a non-protein diet was commenced. In addition, neomycin and lactulose were given to reduce the proliferation of nitrogen-producing organisms. In an attempt to improve the prothrombin ratio, vitamin K was given. He was also carefully monitored to detect complications, such as hypoglycaemia and infection.

These measures appeared to stabilise him, preventing a worsening of the encephalopathy. Over the next week, his liver function showed some improvement and his cognitive function returned to normal. By the end of the week, he was able to take a normal diet again.

He was discharged two and a half weeks after his initial presentation. No satisfactory explanation of where he had acquired the infection was ever discovered.
Figure 1.

Constructional apraxia due to hepatic encephalopathy.

Note: The test involved copying a five pointed star.

Table 1.
Liver function tests during illness.

<table>
<thead>
<tr>
<th>Day</th>
<th>Bili</th>
<th>AP</th>
<th>GGT</th>
<th>PTR</th>
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<td>1</td>
<td>126</td>
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<td>143</td>
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<td>4</td>
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<td>189</td>
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<td>67</td>
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Normal range: Bili 2-17 μmol/l, AP 40-100 u/l, GGT 10-55 u/l, PTR 1.0, ALT 10-40 u/l, Urea 2.5-6.6 mmol/l

Bili: Bilirubin
AP: Alkaline phosphatase
GGT: Gamma-glutamyl transferase
PTR: Prothrombin ratio
ALT: Alanine transaminase
Discussion

Acute hepatitis B infection is generally a self-limiting condition, with complete recovery in the majority of cases. Occasionally fulminant hepatic failure supervenes, carrying a high mortality. Hepatic failure has many complications. Hypoglycaemia may develop as the liver's glycogen stores are depleted. Renal failure may occur secondarily to acute tubular necrosis. Electrolyte and acid-base imbalance such as hypokalaemia or hyponatraemia are common complications. Pneumonia and infections of drip-sites or urinary tract are particular problems of the debilitated patient. Respiratory failure may occur as a terminal event (Kiernan and Ramgapel 1977).

The prothrombin time is a good guide to prognosis. Hepatic synthesis of clotting factors I, II, V, VII, IX and X is impaired, and since most of these factors have short half-lives, rapid depletion occurs and haemorrhage can result. Vitamin K might help restore the prothrombin time, however fresh frozen plasma is often needed.

Hepatic encephalopathy appears to result from the production of ammonia and related compounds by the action of colonic bacteria on nitrogenous waste. Measures aimed at reducing the formation of such compounds include inhibiting the proliferation of bacteria with oral neomycin, reducing the intake of dietary protein, and using histamine antagonists to reduce the risk of gastrointestinal haemorrhage. Lactulose may work by reducing the intraluminal pH, this increases the ionisation of ammonia, in which form it is poorly absorbed.

These measures are supportive, hopefully giving the injured hepatocytes time to regenerate and recover their function. However if the degree of encephalopathy is severe, coma develops, the mortality ranging from 80-90%. More intensive treatment such as the use of corticosteroids, haemodialysis, plasmapheresis, exchange transfusion, animal liver transfusion and charcoal haemoperfusion have not been successful in improving survival (Schiff and Schiff 1982).

Although the patient presented here did develop a minor degree of encephalopathy, it did not progress and he made a good recovery.
This infection is a good example of one that always runs its natural course. The outcome depending upon the virulence of the organism and the effectiveness of the immune response. The damage that occurs to the liver is thought to be mediated, in part, by the immune response. Possibly those patients who develop fulminant hepatic failure have too vigorous an immune reaction to the virus. Conversely those patients who progress to become chronic carriers of the infection may have poor responses. The majority of patients however, will clear the infection, making a good recovery.

References:


A Functional Murmur?

A 41 year old housewife was admitted to the ward complaining of intermittent fevers over the last month. Prior to this she had been quite well. Initially the fever would occur once every few days, although lately it had occurred more frequently, taking longer to resolve. Typically she would awake at 4.00 am drenched in cold sweat. This would pass, but twelve hours later she would have a further fever. On several occasions she had found her temperature to be 39°C. The fever was accompanied by a headache, but no other systemic symptoms. She had not had any rigors.

Recently she had also experienced several episodes of palpitations, taking the form of either a few missed beats, or runs of fast irregular beats.

Although feeling generally unwell, her appetite was good and she had not lost weight.

Three weeks prior to the development of her symptoms she had had multiple dental fillings with no antibiotic prophylaxis. Although previously she had been quite healthy, on probing she revealed that a heart murmur had been accidentally discovered in 1967. This was thought to have been due to mitral valve prolapse, (MVP), and she had been reassured that it was a functional murmur, and that no further action need be taken.

Her drug therapy was limited to aspirin, in particular she had received no antibiotics over the previous three months.

With the exception of her daughter who suffered from paroxysmal tachycardia, her family history was unremarkable.

On examination she looked unwell, with a temperature of 38.7°C. She had slight cervical lymphadenopathy and her spleen tip could be felt. However she had no other stigmata of subacute bacterial endocarditis: there being no finger clubbing, splinter haemorrhages, Osler's nodes, subconjunctival or petechial haemorrhages. Fundal examination was normal, there being no evidence of Roth's spots. She had a tachycardia of 100 beats/min., a thrill could be felt at the lower left sternal edge, and on auscultation an apical, pansystolic murmur (Grade 4/6), was heard radiating to the axilla and also over the lower chest at the back. Dipstick urine analysis
was normal. A full blood count revealed a leucocytosis (11x10^9/l), with 86% neutrophils. Her erythrocyte sedimentation rate was raised at 45 mm/h, although other haematological indices were normal (haemoglobin 12.3 g/dl; platelet count 245x10^9/l). Her liver function tests were mildly deranged, the alkaline phosphatase and gamma-Glutamyl transferase slightly raised at 154 u/l and 60 u/l respectively. Urea and electrolyte concentrations were normal, and an electrocardiogram and chest X-ray unremarkable.

The history of dental work, on a patient with a known cardiac lesion, suggested the diagnosis of subacute bacterial endocarditis (SBE). In keeping with this were the fever, tachycardia, splenomegaly, raised ESR and leucytosis. Serial blood cultures were taken and an echocardiogram performed. This was not helpful however, revealing only slight thickening of the mitral valve leaflets, with no evidence of vegetations. The aortic valve was normal. Further blood cultures were drawn over the next few days, whilst active treatment was withheld in the absence of any worsening of the patient's condition.

On the third day of admission one set of blood culture bottles were reported growing Staphlococcus albus. This is unlikely to cause endocarditis in the absence of a defect in host immunity, and consequently was thought to represent contamination.

By the fourth day of admission, with no positive bacteriology results forthcoming, other possible causes of this patient's pyrexia were considered. An ultrasound scan of her abdomen was performed, demonstrating dilatation of the pelvis and collecting system of the right kidney. This finding raised the ominous possibility that a hypernephroma might be the cause of the symptoms. After two further days, the blood cultures were still negative, and an intravenous urogram was performed. This investigation turned out to be a red herring. Although the ultrasound appearances were confirmed, the dilated pelvis was deemed to represent a normal variation.
Later that day however the diagnosis was made, when fifteen blood culture bottles were reported to be growing an alpha-haemolytic streptococcus, the commonest cause of endocarditis following dental surgery. Intravenous antibiotic chemotherapy was started immediately, with eight megaunits of penicillin and 240 mg gentamicin daily.

The initial regimen was to treat with the penicillin for a full four weeks, discontinuing the gentamicin after two. However after one day on this therapy, it was apparent that peripheral venous access was so limited, that long term treatment by this route would have been impracticable. Consequently an indwelling central venous line was inserted.

Shortly after this a second echocardiogram was performed, this time revealing the presence of a vegetation on a prolapsing leaflet of the mitral valve.

Soon after starting the antibiotics her fever and tachycardia settled and she began to feel much better.

**Discussion**

Mitral valve prolapse (MVP) is a common condition, occurring in 4-6% of the population (Hickey et al., 1985). An increased susceptibility to infective endocarditis has been reported, so that someone with this condition carries a 5-8 times increased risk above normal (Durack, 1985).

In retrospect it was unfortunate that this patient did not receive antibiotic prophylaxis prior to undergoing dental work. However antibiotic prophylaxis for MVP is a contentious issue. Infective endocarditis is uncommon: only 14 in 100,000 patients with MVP develop the condition each year (Hickey, 1985). This low risk raises the question whether prophylaxis would be cost effective: the morbidity so avoided might be outweighed by side-effects such as anaphylaxis. Some authors suggest that prophylaxis should be used only for those patients with MVP and a systolic murmur.
Oakley (1984), advises that only those with both auscultatory and echocardiographic evidence of MVP, need protection. Echocardiographic findings of MVP do not qualify a patient for prophylaxis on their own. However Roucaut et al., (1984) maintain that all patients with MVP should receive protection, whether or not a murmur can be heard.

The problems posed by this patient when considering her antibiotic therapy are illustrative of the way a clinician must evaluate the relative advantages of different regimens. In 1909 infective endocarditis had a mortality approaching 100% (Goodwin 1985). The introduction of penicillin reduced this to 30%, a figure that has remained relatively constant since. To minimise mortality the optimal antibiotic regimen must be selected. A typical example consists of penicillin and gentamicin. Penicillin alone, can be given when the organism is a sensitive viridans group streptococcus, however the addition of gentamicin shortens the duration of therapy from six to four weeks. There is also some evidence that this combination has a lower relapse rate (Garrod et al., 1981). The combination of penicillin and gentamicin has been shown to be synergistic in vitro, and animal models suggest that this also occurs in vivo (Wilson and Geraci 1985).

To give parenteral therapy for four weeks can be difficult, indeed in the patient presented here, a central venous line had to be inserted. Most authorities agree that in view of the seriousness of endocarditis, antibiotics must be given parenterally, however Gray (1981), asserts that when the infection is due to an alpha-haemolytic streptococcus, fully sensitive to penicillin, that treatment can be with oral amoxycillin and probenicid. Guntheroth et al., (1985) also report using this regimen successfully.

This has the advantage that it avoids the potential complications of permanent indwelling lines, and could conceivably be carried out as an out-patient, so avoiding a prolonged hospital stay. Against this treatment though, remains the fact that endocarditis is a potentially fatal illness, and that relapse can have serious consequences.
References

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A Compromised Host

A thirty four year old housewife with chronic myeloid leukaemia (Philadelphia chromosome positive), underwent allogenic bone marrow transplant. Preoperatively she was in good condition, although there was some evidence that her disease was accelerating, possibly undergoing transformation. She received a standard regimen of cyclophosphamide and total body irradiation to ablate her bone marrow, before receiving her graft from her HLA identical brother.

The new marrow recovered very rapidly, so that three weeks after the procedure she had a white cell count of 10x10^9/l and her platelet count was more than 100x10^9/l. A bone marrow aspirate confirmed that the transplant had been succesful, the karyotype of all the cells being male and lacking the Philadelphia chromosome. The only complication during this time was a pyrexia of 39°C., with alpha-haemolytic streptococci being isolated in her blood cultures. Inspite of optimal antibiotic chemotherapy, her fever only settled on the removal of the Hickman line. She was taking prophylactic medication in the form of nystatin, amphotericin, acyclovir, cotrimoxazole and penicillin from the time of the transplant.

Three weeks after the transplant a progressive derangement in her liver function tests was noted (bilirubin 12 μmol/l, alanine aminotransferase 154 u/l, alkaline phosphatase 337 u/l, gamma-Glutamyl transferase 101 u/l). Serological testing for viral hepatitis was negative (Cytomegalovirus, Hepatitis A and B, Epstein Barr virus), as was an ultrasound scan of her liver and biliary system. She refused a liver biopsy and remaining clinically well, was discharged shortly afterwards.

One week later however, she was readmitted with colicky abdominal pain, diarrhoea, nausea and vomiting. She also complained of a burning sensation in her hands and feet. On examination she had a maculopapular rash, with flaking of the the skin on her chest. She also had several small mouth ulcers.

A full blood count showed that the marrow was still functioning
well (haemoglobin 12.6 g/dl, platelets 198x10^9/l, white cell count 9.1x10^9/l). However her liver function tests had become steadily more deranged (bilirubin 19 µmol/l, alanine aminotransferase 306 u/l, alkaline phosphatase 503 u/l, gamma-Glutamyl transferase 177 u/l).

This picture of exfoliative dermatitis, hepatitis, diarrhoea and paraesthesia of the extremities is characteristic of graft versus host disease (GVH). Rectal and skin biopsies confirmed this, showing a lymphocytic infiltration, with death and degeneration of mucosal and epithelial cells.

She was treated with the the immunosuppressive agents azathioprine and prednisolone. The diarrhoea and abdominal pain settled, whilst her skin and liver function tests improved. Inspite of the prophylactic acyclovir and antifungals, both Herpes simplex virus and Candida albicans were isolated from her oral ulcers. However the lesions showed no sign of spreading and she continued on the same treatment.

The immunosuppression was continued and the GVH remained well controlled, with only occasional episodes of diarrhoea. But three months after the transplant she complained of painful dysphagia. Oesophagoscopy was performed, the biopsies revealing multiple pathology. GVH was involving the oesophageal mucosa, with in addition, spores and hyphae typical of C. albicans, and vacuolated cells of a herpetic infection. It being evident that oral acyclovir was not controlling the herpes infection, she was commenced on intravenous acyclovir. Cyclosporin was substituted for azathioprine, and the nystatin and amphotericin continued. Intensive monitoring of sputum, urine, blood and skin was performed, to detect the possible development of systemic candidiasis.

A repeat oesophagoscopy three weeks later, showed a resolution of the herpetic lesions, but persisting GVH and a worsening of the candidiasis. With candida now detected in her urine, the ominous possibility of disseminated candidiasis prompted the decision to treat with intravenous antifungal agents.
She was started on flucytosine and shortly afterwards her dysphagia resolved. However at this point a further complication arose, when her urea, which had been stable at around 6 mmol/l, began to rise, reaching 12.5 mmol/l. This was paralleled by a rising creatinine, from 70 umol/l to 168 umol/l. This deterioration in renal function was attributed to the combined nephrotoxicity of amphotericin and cyclosporin. An increase in her fluid intake enabled a stable, although high, level of urea to be maintained.

She continued on the immunosuppression, precariously poised between life-threatening GVH and the possibility of developing a fatal opportunistic infection, able to take advantage of her diminished immunological function.

Discussion

This patient demonstrates the spiral of complications that can ensue as ever more potent treatments are employed to deal with serious problems. The bone marrow transplant can cure an otherwise fatal disease such as chronic myeloid leukaemia. However GVH is a common problem, requiring immunosuppression to control it. Cellular immunity can be so depressed that organisms, normally of low pathogenicity, can cause grave infections. Even without added immunosuppression recipients of bone marrow transplants are at particular risk of infection. In one series 50% of patients developed septicaemia. Gram negative bacilli and fungi being responsible for the majority of cases (Winston et al., 1979). Pneumonia occurred in 51% of patients: cytomegalovirus, Pneumocystis carinii and various fungi were the commonest causative agents. Oral candidiasis and herpetic stomatitis are often troublesome, and occasionally oesophageal involvement occurs, as happened to the patient presented above.

Disseminated fungal infections are an important problem, always associated with a high mortality. Diagnostic delay exacerbates this problem, it being difficult to decide when invasion is taking place. Because of this, screening procedures, in which various sites
are periodically sampled to determine the resident flora, should be employed. In addition, urine and sputum should be monitored, and at the first indication of dissemination, vigorous intravenous therapy with antifungal agents should be employed.

Cytomegalovirus is a particular risk for transplant patients. It may cause an interstitial pneumonitis, with a 60-70% mortality (Meyers et al., 1983). It can also cause hepatitis, hence the concern when this patient's liver function tests first became deranged. There are various possible sources of infection. The virus may be transmitted from the environment, the patient's contacts or infected blood products. It may also arise from reactivation of an endogenous, latent infection. The patient presented here was fortunate to avoid infection with the virus, and various measures may have contributed to this. She was seronegative for cytomegalovirus before the transplant, and so probably did not have a latent infection. Any blood products that she received were screened for the virus before transfusion, and in addition, she received anti-cytomegalovirus immunoglobulin as prophylaxis.

In summary, the clinical course of this patient is a good example of the problems that can arise when a host's immune defences are disrupted.

References


Winston DJ, Gale RP, Meyer DV, Young LS; Infectious complications of human bone marrow transplantation. Medicine 1979 58, 1-31
The Missed Diagnosis

An eighty one year old man was admitted complaining of chest and upper abdominal pain. He had been unwell with anorexia and headache all day, when the pain had started suddenly in the afternoon. It had spread across the lower part of his chest and upper abdomen, but there was no radiation, aggravating or relieving factors and no associated symptoms such as nausea, vomiting, breathlessness, cough or sputum.

His health was good, although he suffered from arthritis, he was active and enjoying his retirement, having worked as a decorator. His drug therapy was limited to indomethacin and nitrazepam. He drank moderate amounts of alcohol, but had not smoked since his schooldays.

On examination he had a temperature of 38.9°C., with a tachycardia of 100 beats/min. Although he was neither tachypnoeic nor cyanosed, bilateral basal crepitations were heard at both bases on auscultation, with the suspicion of a pleural rub on the left. His abdomen was obese, with prominent epigastic tenderness, guarding in his right hypochondrium and positive for Murphy's sign. His liver was not palpable, no masses could be felt, his bowel sounds were normal and a rectal examination was unremarkable. Both his cardiovascular and neurological examinations were normal.

His blood biochemistry revealed hypokalaemia (2.6 mmol/l) and a raised urea (9.3 mmol/l), but was otherwise normal. A full blood count showed a mild macrocytosis (MCV 104) but normal haemoglobin and white cell values (14.5 g/dl and 4.9x10^9/l respectively). In addition his liver function tests were abnormal (albumin 29 g/l, total protein 53 g/l, alkaline phosphatase 227 u/l, gamma-glutamyl tranferase 57 u/l, alanine transaminase 61 u/l, bilirubin 17 μmol/l). An electrocardiogram showed T inversion in his inferior leads but no other abnormalities. A chest X-ray was also performed, with appearances suggestive, although not gross, of left, basal consolidation.

In view of his abdominal findings, a working diagnosis of acute cholecystitis was made, and he was started on intravenous cefuroxime.
He was still febrile on the following day, becoming confused and disorientated overnight, claiming to have been in hospital for four days. The abdominal tenderness was still evident and so metronidazole was added to his regimen to cover the possibility of anaerobic sepsis. By the fourth day of admission he was still ill. A second chest X-ray demonstrated an effusion at the left base, as well as the consolidation seen previously. In the light of this his diagnosis was changed to pneumonia, and the cefuroxime was replaced by augmentin. Serological screening was performed to exclude atypical pneumonia, but as he was not producing sputum, culture for the organism was not possible. A further two days passed, still without improvement. A pleural aspirate was performed, the protein concentration of 30 g/l indicating an exudate. However bacteriological and cytological examination were negative. Erythromycin was added empirically to his regimen, to cover mycoplasma or legionella infection. After two days on erythromycin, his pyrexia had settled and a chest X-ray showed a resolution of his effusion. He made a steady recovery and was on the verge of discharge, when the titre of antibody against *Legionella pneumophila* was returned at a very high level. Although a four fold rise in paired serum samples is stronger evidence of recent infection, a single high titre is generally adequate for diagnosis, since only 0.4% of the Scottish population have backround titres in this range. Fallon (1982), calculates that a single high titre can be taken as evidence of recent infection (p<0.001).

The patient was discharged to complete a course of erythromycin.

**Discussion**

*Legionnaire's disease is often a difficult diagnosis to make.* In the patient presented above, the extra-pulmonary symptoms diverted attention from his pneumonia. It was only when he failed to respond to convetntional antibiotics that it was realised that there was significant pathology in his chest. In retrospect this patient did have several features characteristic of *Legionnaire's disease*. Neurological symptoms such as confusion
and disorientation are common. Other features, not seen in this patient, include: hallucinations, stupor, grand mal epilepsy, cerebellar and other focal signs. Headache is common, as are nausea and vomiting. Abdominal pain occurs occasionally. Typical laboratory findings include the abnormal liver function tests, as occurred in this patient. Hyponatraemia and hypophosphataemia also occur. Failure to respond to most antibiotics, with the exception of erythromycin and rifampicin is also typical (Edelstein and Myer 1984).

A feature contributing to the difficulty of diagnosis is the fastidious nature of the organism, requiring special culture media for its growth. Although it can be grown from respiratory secretions, diagnosis is commonly made retrospectively by serological methods. A fluorescent antibody technique can allow rapid diagnosis, if tissue or secretions are available.

A further feature that complicates diagnosis, is that the epidemiology of the disease is largely unclear. Although dramatic outbreaks have occurred, in the setting of which diagnosis is easier since the index of suspicion is higher, in Scotland, the majority of cases are isolated incidents (Fallon 1982). Airborne transmission is responsible, and cooling towers, air conditioning and shower units are sometimes associated. The disease has a peak incidence in the autumn and summer (this patient presented in the spring), with a predilection for middle-aged or elderly men. Other predisposing factors include: heart and lung disease, immunosuppression and malignancy. Smokers are also more prone to develop the disease, (Pang and Spiro 1982).

The true incidence of the disease is also unclear. Many cases go undiagnosed, unless legionella antibody is specifically sought. In one prospective study, Legionnaire's disease was the second most common community acquired pneumonia, accounting for 15% of all pneumonias (Editorial, Lancet 1983).

This patient demonstrates that the diagnosis of Legionnaire's disease is easily missed, and in view of its high mortality and frequency, the diagnosis should be considered in all patients presenting with a community acquired pneumonia, particularly
if, they should present with prominent extra-pulmonary manifestations.

References


Editorial. How common is Legionnaire's disease? Lancet 1983 i, 103-104


A Complicated Sore Throat

A thirty nine year old painter was admitted with pyrexia, rigors and loin pain. He had been well until two days previously, when he developed a sore throat and fever. Subsequently he had some loin pain and noted that his urine was darker than normal. On the day of admission he had a rigor and thought that he was passing reduced amounts of urine.

Two years previously he had experienced a similar episode, when a sore throat was followed by loin pain and haematuria. This was managed by his General Practitioner, his symptoms resolving within a few days on treatment with antibiotics.

Three years before he had undergone renal angiography, when he had frank haematuria following a road traffic accident. This investigation had been normal.

He was well otherwise, his drug intake limited to a few aspirin since the onset of his fever. He drank an average of twelve units of alcohol a week and smoked twenty cigarettes a day. He had no family history of significance.

On examination he had a temperature of 39°C., his throat was inflamed and a tender cervical lymph node could be felt on the right. His blood pressure was 140/80 and with the exception of minimal bilateral loin tenderness, he had no other abnormalities, in particular there being no evidence of oedema or periorbital swelling. Urine analysis and microscopy revealed the presence of protein (+++), blood (++) and red cell casts.

His full blood count showed a neutrophil leucocytosis (white cell count 19.4x10^9/l; the differential 82% neutrophils). His haemoglobin was 16.7 g/dl.

Both his urea and creatinine were raised (8.4 mmol/l and 154 umol/l respectively), but his electrolytes were normal.

The history, examination and laboratory results pointed to a glomerulonephritis, and given the history of a similar previous episode, as with this admission, the onset of symptoms coincidental with a febrile upper respiratory illness, a diagnosis of Berger's Disease (IgA Nephropathy) seemed likely.
A Group A beta-haemolytic streptococcus was isolated from his throat. This was treated with penicillin, the sore throat and fever resolving. The glomerulonephritis was managed conservatively and over the next few days, a period of oliguria was accompanied by a rise in his blood urea and creatinine levels (Figure 2). A twenty four hour urine collection the day after admission gave a creatinine clearance of 56 ml/min, and a non-selective protein loss of 4.2 g/day. Although this protein loss is in the nephrotic range, it is not incompatible with the diagnosis of Berger's disease, since 10% have losses in this range. Along with this loss, his plasma albumin concentration dropped from 40 g/l on admission, to 33 g/l on the sixth day. Serum complement components and immunoglobulins were found to be normal, with the exception of a marginally raised IgA level, (4.47 g/l; Normal range 0.5-4.0 g/l), evidence in keeping with the diagnosis.

His clinical course was uneventful, being normotensive throughout, with no evidence of oedema. A diuresis followed, reaching a peak on the eighth day, and his urinary protein loss declined. Once his glomerular function was improving he underwent renal biopsy, which unexpectedly failed to confirm the diagnosis of Berger's disease, revealing instead a non-specific picture, more in keeping with a post-infective glomerulonephritis. He was discharged once the haematuria and proteinuria had resolved.

Discussion

Many infectious agents are associated with glomerulonephritis, the prototype perhaps being that that follows ten to twelve days after a beta-haemolytic streptococcal sore throat (or skin infection in developing countries). Although it can occur in adults this is predominantly a disease of childhood, in whom the course is generally self-limiting. In adults the illness can be more severe, tending to have a poorer prognosis. Acute proliferative glomerulonephritis can follow infections due to the Epstein-Barr virus, Varicella-Zoster, typhoid fever,
Figure 2.
Plasma urea and creatinine concentrations with urine output during the course of acute glomerulonephritis.
pneumococcal infection, infective endocarditis and toxoplasmosis. The clinical picture can vary from asymptomatic haematuria and proteinuria to acute renal failure. The nephrotic symptom can occur in the course of infection with Quartan malaria and secondary syphilis.

IgA nephropathy is also associated with infection, although the nature of the infective agent is less clear. In contrast to the post-infectious glomerulonephritis, the nephritis typically occurs at the height of a febrile illness, rather than a week or two later. The infection possibly acts as a non-specific initiator of the nephritis, since it can be induced by other stimuli such as exercise in susceptible individuals.

The patient presented above did not fall into any classical diagnostic group. Although his history was typical of Berger's Disease, the biopsy was not compatible with this. The biopsy result taken with the isolation of the beta-haemolytic streptococcus suggested the diagnosis of post-infective glomerulonephritis. However the speed of development of the renal lesion is not characteristic of this disease. Indeed Whitley et al., (1984) state that the diagnosis can never be one of post-streptococcal glomerulonephritis, if the interval between infection and onset of the nephritis is less than four days. Whatever the diagnosis, this case is a good example of how a microorganism can interact with the immune system, to produce disease in the host, even after the infection has been eradicated.

**References**


A Simple Goitre?

A thirty nine year old clerical assistant was referred complaining of a tender neck swelling, a sore throat and dysphagia. She had first noticed the swelling two weeks previously when she experienced difficulty fastening a necklace. Subsequently she developed a sore throat, associated with painful dysphagia, which her General Practitioner had treated initially with penicillin and then cotrimoxazole. However her symptoms persisted and she was referred to hospital.

She had no symptoms of thyroid disease, her weight was steady and she had no menstrual problems. She was on no medication apart from the antibiotics. Previously she had been well, although one of her three pregnancies had resulted in a miscarriage. An aunt had suffered from some form of thyroid complaint.

On examination, she had a tender, diffusely enlarged thyroid, which was soft in consistency and moved on swallowing. There was no bruit, nor did she have any signs typical of thyroid disease. She was afebrile, had no lymphadenopathy and her throat was not significantly inflamed.

A diagnosis of subacute thyroiditis seemed likely. This may present as a tender goitre, often in association with symptoms of an upper respiratory tract infection. To confirm the diagnosis, thyroid function tests, a radioactive thyroid uptake scan, thyroid auto-antibody studies and a viral serological screen were performed. (Table 2).

Table 2.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Plasma total thyroxine</td>
<td>74 (70-150 nmol/l)</td>
</tr>
<tr>
<td>Plasma total triiodothyronine</td>
<td>1.7 (1.1-2.8 nmol/l)</td>
</tr>
<tr>
<td>$^{131}I$ uptake scan</td>
<td>38 (10-40%)</td>
</tr>
<tr>
<td>Thyroid auto-antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Viral serology: adenovirus, coxsackie and mumps</td>
<td>Negative</td>
</tr>
</tbody>
</table>
The results of these investigations did not, however, support the diagnosis. In subacute thyroiditis the iodine uptake is usually low, thyroid hormones tend to be elevated in the early stages, returning to normal in four to six weeks, and thyroid auto-antibodies can appear transiently. None of this was found in this patient, and she was sent home to be reviewed in two weeks.

At review she still complained of a sore throat, but in addition had developed a hoarse voice. The gland was larger and more tender, and now cervical and axillary lymphadenopathy could be felt, as well as a three centimetre enlargement of the liver. Once again she was found to be euthyroid, but other investigations revealed a raised erythrocyte sedimentation rate (27 mm/h), and a low white cell count of 3.9x10^9/l. A monospot test was negative and her liver function tests were normal. Again she was discharged, to be followed-up in two weeks.

She was still unwell when she was seen again. Her throat was now exquisitely tender and she complained of night sweats, anorexia and general malaise. On examination the previous findings were still present, but her posterior cervical lymph nodes were particularly prominent, her liver was now tender to palpation and a spleen tip could be felt.

A full blood count gave a white cell count of 8.0x10^9/l with many atypical lymphocytes. Liver function tests were also repeated, showing the alanine aminotransferase raised at 570 µ/l, although the other parameters were normal. The Paul-Bunnell test was positive, IgM antibody specific for Epstein-Barr virus was detected and IgG antibody was weakly positive.

The patient had infectious mononucleosis. Typical features are general malaise, fever, a sore throat, generalised lymphadenopathy, although the posterior cervical nodes can be very large. In many patients the spleen is palpable, and as many as 50% will have biochemical evidence of hepatitis. The IgM specific for the virus indicates recent infection. However the tender goitre was still unexplained and she was admitted to the ward for further investigation.
A TRH stimulation test was performed giving a normal TSH response. She remained euthyroid, her auto-antibody screen was still negative and a second radioactive thyroid scan was again normal at 37%.
The goitre persisted and the scan confirmed the goitre, showing areas of increased uptake. Her liver function tests returned to normal and the IgM to Epstein-Barr virus disappeared, indicating recovery from the acute infection. Once the sore throat had resolved she was discharged from the ward.

When reviewed one month later her liver function was normal, she was euthyroid but the goitre had persisted and was still moderately tender. The tenderness disappeared but several months later the goitre was still in evidence. A decision was made to treat this as a simple goitre and she was commenced on 0.15 mg thyroxine/day. "TSH irma" confirmed adequate suppression of thyroid stimulating hormone and the goitre has since decreased in size.

Discussion

This patient presented with many features typical of subacute thyroiditis. A tender thyroid that enlarges over a short period, frequently accompanied by systemic upset is typically described (Levine 1983). However the results of the laboratory investigations did not show the features characteristic of the disease. Other possible causes of a painful goitre would include haemorrhage into a nodular goitre, a rapidly enlarging anaplastic carcinoma of thyroid and occasionally Hashimoto's thyroiditis.
The laboratory results are most compatible with a simple goitre. A normal plasma thyroxine and triiodothyronine, with a normal TSH response to TRH, are in keeping with this. So to, is the result of the thyroid scan. However a simple goitre should not be tender unless there has been haemorrhage into a cyst or adenoma, in which case the pain should diminish over several days. This patient's tenderness persisted for several months.
A carcinoma of thyroid can be excluded on the long history, clinical examination and the thyroid scan. Hashimoto's thyroiditis may be associated with some neck discomfort, slight dysphagia and diffuse thyroid enlargement. Although the enlargement tends to be gradual, it can occasionally occur rapidly, so mimicking subacute thyroiditis (Wilson and Foster 1985).
However the complete absence of thyroid auto-antibodies makes this diagnosis unlikely.

The true nature of this patient's goitre remains unknown. A biopsy might have resolved the problem, demonstrating for instance, the giant cells typical of subacute thyroiditis. This investigation was not performed.

It is intriguing that the patient developed infectious mononucleosis (I.M.) shortly after presenting with the goitre. Viral infection has frequently been associated with subacute thyroiditis, the commonest organisms being coxsackie, mumps and adenovirus. However, there are a few reports of subacute thyroiditis being associated with I.M. due to the Epstein-Barr virus (Fennell and Tomkin 1978). Although the simultaneous presentation of the tender thyroid and I.M. may have been fortuitous in the case of the patient presented here, a unifying diagnosis would be to postulate that in this case infection with the Epstein-Barr virus, resulted in an atypical form of subacute thyroiditis. This would account for the normal thyroid function tests.

Infectious mononucleosis is a common disease, usually running a predictable course. Complications occasionally occur, such as splenic rupture, auto-immune thrombocytopenia, nephritis, meningitis and pancreatitis, and in view of the multi-organ involvement, it is not inconceivable that this patient's thyroid complaint was related to the infection.

In all other respects the course of the I.M. was typical. There is often a delay between onset of symptoms and the production of heterophil antibody. This explains why the patient's monospot test was initially negative. A subclinical hepatitis is common, as in this patient, and it is rare for there to be significant impairment of hepatic function.

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Conclusion

Although the great scourges of the past such as smallpox, diptheria and polio are unlikely to be major problems in Britain in the future, infections continue to present the clinician with challenging problems. New diseases are recognised in the form of *Legionella pneumophila* and the Human T Cell Leukaemia Virus, requiring novel approaches to diagnosis and therapy. The spread of drug resistance amongst bacteria necessitates the development of new antibiotics. The increasing number of patients with compromised immune function allows organisms, previously of little importance as pathogens, to cause significant disease. Man's immune system will continue to be a major determinant to the outcome of infection. The field of immunomodulation has enormous potential in terms of therapy, but is as yet little exploited. The immune system might be enhanced by the use of lymphokines such as the interferons or interleukins, both of which can be produced in large quantities by recombinant DNA technology. Synthetic agents might also be capable of boosting the immune response: inosine is one drug for which such claims have been made. Alternatively, developments in cell culture technique might allow the removal of host immune cells, the selection and proliferation *in vitro*, of cells specifically directed against an invading microorganism, and the subsequent reinfusion of greatly increased numbers of immunocompetent cells. By these measures a feeble immune system might be aided, so overcoming an otherwise fatal infection. There is therefore much scope for research and development in the field of infectious diseases.
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