Behçet's disease with endocarditis and the Budd-Chiari syndrome

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SUMMARY Endocarditis of the mitral and aortic valves is described for the first time in a patient with Behçet's disease. A second patient had minor changes in the mitral valve similar to that seen in the vasculitis which occurs in this condition. Valvulitis in Behçet's disease probably has the same pathogenesis as the vasculitis. The second patient also had a rare combination of Behçet's disease and the Budd-Chiari syndrome, and the necropsy findings are described.

In 1937, Behçet described a syndrome of relapsing orogenital ulcerations and ocular lesions such as iritis and hypopyon. Many other features have since been added to this triad, and recent reviews have emphasised the systemic nature of this condition.^{1 2}

Cardiac manifestations are among the least common in Behçet's disease. They are pericarditis,³ ECG changes of 'carditis',^{4 5} and conduction defects.^{6 7} The only necropsy descriptions are those of McMenemy and Lawrence,⁸ who described 'myocardial degeneration' in one patient, and of Davies,⁹ who described a patient with mural thrombosis of the right ventricle associated with pulmonary lesions. Endocarditis affecting heart valves has not been reported in Behçet's disease.

In contrast, vascular lesions are common in this condition, and there is evidence to suggest that a vasculitis is the basic underlying pathology.¹⁰ These lesions include superficial thrombophlebitis,¹¹ thrombosis of large veins,^{12 13} and arterial aneurysms.^{14 15} The large veins involved have usually been the venae cavae and main tributaries, and only four cases have involved the hepatic veins with production of the Budd-Chiari syndrome. Three of these had no postmortem examinations.^{13 16 17} The fourth case, with necropsy findings, has been reported in Japanese.¹⁸

This paper concerns two patients with Behçet's disease, one of whom had an associated endocarditis, and the other the Budd-Chiari syndrome.

Case reports

CASE 1

An 18-year-old woman had had numerous admis-

sions to hospital since childhood because of recurrent mouth and vulval ulcerations, recurrent skin sepsis, dry eyes, and facial swellings. These episodes used to be self-limiting and lasted about two months. She had had a tonsillectomy at 5 years of age.

A diagnosis of Behçet's disease was first made when the patient was 16 years old. At the time she was found to have splenomegaly, and investigations were Hb 13.7 g/dl, total WBC $7.5 \times 10^9/l$, polymorphs 41%, lymphocytes 53%, monocytes 6%. Many of the lymphocytes appeared atypical. Platelets were $200 \times 10^9/l$. Other investigations, including chest x-ray, plain x-ray of abdomen, oesophagoscopy, and splenic biopsy, were normal. The patient responded dramatically to prednisone, 40 mg per day. This was later reduced to 15 mg per day, but all subsequent attempts to stop it resulted in relapse.

Two years later the patient was clinically Cushinoid and still liable to recurrence of orogenital ulcers whenever steroid withdrawal was attempted. During one such relapse she developed a tachycardia of 110 to 120 per minute, and this continued despite a remission of the orogenital ulcers. Blood pressure was normal, as was an electrocardiogram apart from showing tachycardia.

The patient's final admission nine months before death was for parotitis with overlying cellulitis. Aphthous mouth ulcers were also present, but these appeared to be healing. An attempt to lower the dose of prednisone resulted in a relapse of mouth ulceration, which persisted despite the reintroduction of steroid therapy in doses of 60 to 80 mg daily. A 'honeycomb' pattern was seen on chest x-ray at this time. Three months later the patient developed a staphylococcal pneumonia complicated by pneumothorax. Blood cultures were negative. One month later she had three episodes of haematemesis and

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melaena. Blood coagulation screen was normal. Gastroscopy showed several small gastric ulcers, one of which was submitted to biopsy. Histology of this showed a benign ulcer with two small, thrombosed vessels in the submucosa and chronic gastritis in the neighbouring mucosa. Investigations at this time included: Hb 9 g/dl, total WBC 1 to 2×10^9 /l, platelets 103 to 143×10^9 /l. Examination of the bone marrow showed gross dyserythropoiesis despite normal B₁₂ and folic acid levels. There was also a marked increase in histiocyte-like cells and marked erythrophagocytosis. Bilirubin $26 \mu\text{mol/l}$, alkaline phosphatase 300 IU , ALT 190 IU , LDH $> 600 \text{ IU}$, HBD 1290 IU .

Plasma electrophoresis was normal; antinuclear factor was negative. Blood urea and electrolytes were normal. A striking feature throughout this admission was a tachycardia of around 130 per minute and a fluctuating pyrexia. Blood cultures at this time were also negative. A few weeks before death a transient 'haemic' murmur was heard. Signs of renal damage now appeared in the form of severe proteinuria and hyaline and granular casts in the urine. In the last three days of life, the patient developed signs of cardiac failure with raised jugular venous pressure, pulmonary crepitations, peripheral oedema, pleural effusions, and gallop rhythm.

Necropsy

The heart weighed 255 g and showed multiple, small, soft, pale yellow lesions on the free ends and ventricular surfaces of the mitral and aortic valves. None measured more than 0.2 cm. The remainder of the heart was normal macroscopically. A small pericardial effusion was present. Histologically, the valvular lesions showed replacement of the inferior (ventricular) half of the cusp by pink granular debris and a dense pleomorphic mononuclear inflammatory infiltrate. Only an occasional polymorphonuclear leucocyte was present, and no fibrin was seen in the sections examined. This process had penetrated deep to the elastica of the valve and extended from the origin to about halfway along the length of the cusp (Fig. 1). Gram and PAS stains for bacteria and fungi were negative, and a swab taken at necropsy was sterile. There was no evidence of previous rheumatic valve disease. The myocardium showed widespread focal myocardial fibre degeneration, and there was a mononuclear infiltrate in the myocardium, in the epicardium, in the intima of the aorta, and around its adventitial vessels.

The trachea and bronchi showed extensive ulceration. The lungs contained areas of consolidation and small thromboemboli in the left lower lobe. The source for the latter appeared to be the ovarian veins which were thrombosed. Histologically, the

Fig. 1 Case 1. Aortic valve cusp showing the non-specific chronic inflammatory cell infiltrate replacing the lower (ventricular) half of the cusp (long arrow). The surface endothelium of the arterial side is just visible (short arrow). (Original magnification Haematoxylin and eosin $\times 250$).

bronchi were dilated and showed numerous areas of necrosis of the wall. Many contained fungal mycelia consistent with *Candida albicans*. Where the latter were present, necrosis, debris, and inflammation extended into the lung tissue and involved the walls of some pulmonary veins with resulting thrombosis. Many alveoli contained a fibrin exudate and a polymorphonuclear and mononuclear inflammatory infiltrate including macrophages with foamy cytoplasm. Several sections showed hyaline membranes, and these were most marked where there was associated interstitial fibrosis and lymphocytic infiltrate. There was also marked alveolar cell hyperplasia in these areas (Fig. 2).

The left parotid gland was enlarged and histologically showed dilated acini, focal necrosis and a non-specific chronic inflammatory infiltrate. The

Fig. 2 Case 1. Lung showing prominent hyaline membranes lining many of the alveoli (arrows). There are areas of alveolar cell hyperplasia and a mild chronic inflammatory cell infiltrate. (H and E $\times$ 100).

oesophagus contained two ulcers, 2.5 cm diameter, which had penetrated through the muscle coat. An accompanying chronic inflammatory infiltrate extended to the adjacent trachea. Some blood vessels in the floor of the ulcer were thrombosed but there was no arteritis. Five similar ulcers were present in the stomach. The uninvolved gastric mucosa showed fewer inflammatory cells than usual, but deep in the mucosa and in the upper submucosa there were several large, pleomorphic cells with hyperchromatic nuclei and occasional phagocytosed basophilic granules.

The liver showed centrilobular congestion and focal fatty change. The lobules showed a very occasional necrotic hepatocyte with a mononuclear response. Portal tracts contained a non-specific chronic inflammatory cell infiltrate. Some Kupffer cells showed erythrophagocytosis. Around one central vein there was an area of coagulative necrosis with nuclear debris and a polymorphonuclear reaction. Three collections of cells were grouped around this area, one in a portal tract. These cells were large, pleomorphic, and hyperchromatic; some were multinucleate and one showed an abnormal mitosis (Fig. 3).

The spleen was enlarged (560 g) and showed atrophic lymphoid follicles and a 3 cm area of

necrosis. At the periphery of the latter there were pleomorphic hyperchromatic cells similar to those seen in the liver and stomach. A section of a lymph node also showed extensive necrosis with peripheral, pleomorphic, hyperchromatic cells. The appearances strongly suggested malignant lymphoma but the cellular preservation was too poor to allow accurate classification. The bone marrow showed marked erythroid hyperplasia and reduced myeloid series. Megakaryocytes appeared normal. No erythrophagocytosis was seen and no abnormal infiltrates.

Sections of the thrombosed vessels in the parovarian region showed old and recent thrombi in arteries and veins and extensive inflammation in the fat and voluntary muscle. This inflammatory infiltrate was non-specific and was similar to that seen on the heart valves, in the parotid, the oesophagus, and other sections.

There were some scattered lymphocytes in the thyroid and adrenal glands and marked atrophy of the latter, which was presumably due to the prolonged steroid therapy. The kidneys showed occasional microscopic cortical scars and pink protein material in the tubules.

The brain and spinal cord appeared normal macroscopically. Sections of the brain (Dr JJ Dinn) showed non-specific changes in the frontal, parietal,

Fig. 3 Case 1. Liver with a portal tract infiltrated by large, hyperchromatic, pleomorphic cells. These were seen elsewhere in the liver and in other organs (see text) and were thought to represent malignant lymphoma. (Original magnification H and E $\times$ 500).

and temporal cortices. These consisted of disruption of the normal architecture and loss of neurones with replacement by haphazardly arranged, large, plump Alzheimer type II astrocytes and associated elongated ('cigar-shaped') microglia. Blood vessels appeared normal, and the meninges showed only some oedematous swelling. The spinal cord appeared normal histologically.

CASE 2

A 24-year-old male clerk was referred to hospital because of hepatomegaly and distended superficial abdominal and thoracic veins. The latter had been present for four months. He had been off work for eight months because of thrombophlebitis, mouth ulcers, depression, and increasing fatigue. He had been attending three different doctors, and medication had included amitriptyline and ampicillin. The patient smoked 30 cigarettes per day, had smoked marijuana, and had a high alcohol intake. There was no history of intravenous drug injections.

On examination the patient appeared very agitated and pale and had a tachycardia of 120 per minute. He was not clinically jaundiced. The mouth was odorous and the tongue coated but no ulcers were seen. He refused genitourinary examination. The abdomen was distended, and collateral veins on the abdominal wall and chest wall were promi-

nent. The liver was enlarged but no ascites was detected.

The patient refused hospitalisation but was admitted two days later jaundiced, in prehepatic coma, and with more marked hepatomegaly. The skin of the scrotum and adjacent medial part of the thighs was very red and inflamed but the patient denied any related symptoms. Tachycardia was still present and there were crepitations in both lungs. Full blood count, urea, electrolytes, calcium, phosphorus, and blood glucose were normal. Total plasma protein was normal but albumin was reduced to 29 g/l. The bilirubin was 108 μ mol/l, alkaline phosphatase 150 IU/l, and AST 201 IU/l. The urine contained urobilinogen and a small amount of bile. Wassermann reaction, Kahn and Reiter's tests were negative. A chest x-ray showed a raised dome of the right diaphragm.

The clinical diagnosis was hepatic failure of an unknown aetiology, but possibly due to viral hepatitis. The patient was given intravenous nutrition but died three days after admission.

Necropsy

In addition to the clinical signs described above, tiny punctate marks were noted on the legs. The serous cavities contained small effusions, and there were petechial haemorrhages over their surfaces.

The entire inferior vena cava, both common iliac veins, and femoral and popliteal veins were occluded by organised thrombus, brownish-grey and very firm, with numerous tiny recanalising vessels. Both renal veins were similarly occluded. This process extended into both hepatic veins and involved most of the branches in both lobes of the liver, especially the right. All these vessels showed thickening of their walls up to 1.5 mm by greyish-white tissue. Several large hepatic veins were thin-walled and contained recent antemortem thrombus. Recent thrombus also extended from the inferior vena cava into the right atrium. The heart and the rest of the vascular tree, including the portal venous system, appeared normal.

The liver weighed 2100 g, and the right lobe was markedly enlarged with rounded borders and a dark reddish-purple, intensely congested cut surface. The left lobe was relatively small and had a wrinkled capsule but also showed similar intense congestion on section. The gall bladder and biliary tree were

normal. The spleen weighed 280 g and was congested; there were a few enlarged lymph nodes in the porta hepatis and marked pulmonary oedema with areas of haemorrhage. Other organs were normal macroscopically but the central nervous system was not examined.

Histologically, the liver showed intense centrilobular congestion with infiltration of the liver trabeculae by red blood cells. There was extensive centrilobular necrosis and collapse of reticulin with a scattered infiltrate of polymorphs. In some sections only small periportal islands of liver cells survived. Large (1 cm diameter) hepatic veins were occluded by recanalised, organised thrombus, and there was a slight infiltrate of lymphocytes in their walls. Medium-sized hepatic veins were occluded by recent thrombus but the smallest veins were patent. Section of the main right hepatic vein showed recanalised organised thrombus and superimposed recent thrombus where it joined the inferior vena cava. There was a lymphocytic infiltration in the wall (Fig. 4). The adjacent

Fig. 4 Case 2. Section of right hepatic vein at its junction with the inferior vena cava. The wall of the vein (W) is infiltrated by lymphocytes. The lumen is filled with organised thrombus in the form of cellular dense connective tissue with some small recanalising vessels (arrow). There is recent thrombus (T) projecting into the lumen (L) of the vena cava. Strands of fibrin (F) are seen. (H and E $\times 40$).

liver tissue showed similar changes to those described above but to a much less marked degree. Severe cholestasis was seen in these areas, however, which was not present in the other sections. Multiple sections of the occluded systemic veins showed recanalised, organised thrombosis composed of dense collagenous tissue in which were numerous small vessels with smooth muscle in the wall and larger thin-walled vessels. Patchy haemosiderin deposits were present. The walls of these veins showed patchy fibrosis extending into the adventitia and focal collections of lymphocytes both here and in the organised thrombi. Many small veins and venules in the nearby fatty tissue showed intimal cellular proliferation and adventitial fibrosis, some of the latter extending into the surrounding fat with occasional lymphocytic foci, plasma cells, and histiocytes. Similar changes were seen in small veins and venules in the perinephric and periadrenal fat.

A slight infiltrate of lymphocytes was noted in the mitral valve with plump mononuclear cells in the subendothelium, and swollen endothelial cells were present on the surface. Several foci of individual myocardial cell degeneration were noted with a mild mononuclear cell infiltrate and also in the connective tissue around capillaries and small arterioles. These minor changes were confined to the subendocardial

region.

Section of the lower end of the oesophagus showed a large submucosal vein containing mural thrombus overlying an area of severe phlebitis. The infiltrate of polymorphs, lymphocytes, and histiocytes in the wall extended into the adjacent submucosa, muscularis mucosae, and lamina propria but the overlying epithelium was intact. The gall bladder showed subserosal fibrosis and a lymphocytic infiltrate.

The lungs showed aspiration pneumonia and haemorrhagic oedema. Despite the thrombosed renal veins, the kidneys were normal histologically apart from a tiny cortical scar in one section. The spleen was normal histologically, the lymph nodes showed non-specific reactive changes, and the bone marrow showed myeloid hyperplasia but with reduction in the number of megakaryocytes. The adrenal glands showed stress changes.

Sections of the reddened skin of the thighs showed an organised thrombus in a large subcutaneous vein. Capillaries in this area and in the dermis had plump endothelium and a few surrounding lymphocytes. A scattering of lymphocytes was also present in an area of condensed dermal collagen. There was parakeratosis of the overlying epidermis and a small intraepidermal bulla containing polymorphonuclear leucocytes (Fig. 5). Sections of the punctate lesions

Fig. 5 Case 2. Skin from erythematous area of thigh. There is parakeratosis and a small intraepidermal bulla to the right of centre. The dermis shows a mild non-specific lymphocytic infiltrate. (Original magnification H and $E \times 125$).

on the skin of the legs showed slight upper dermal oedema and an increase in capillaries with plump endothelium and perivascular lymphocytic foci (Fig. 6).

The following organs were also examined histologically and found to be normal: bronchus, jejunum, ileum, pancreas, prostate, thyroid, and voluntary muscle.

Discussion

The diagnostic criteria for Behçet's disease can be grouped into major and minor manifestations. The major criteria are: buccal ulceration, genital ulceration, eye lesions, and skin lesions. The minor criteria are: gastrointestinal lesions, thrombophlebitis, cardiovascular lesions, arthritis, central nervous system lesions, and family history. A diagnosis of Behçet's disease can be made if a minimum of three of the major criteria, or two major and two minor criteria, are present.¹⁹ A diagnosis of Behçet's disease is established in our first patient by the presence of three major criteria: buccal ulceration, genital ulceration, and skin lesions (recurrent skin sepsis). The second patient had Behçet's disease on the basis of two major criteria (buccal ulceration and skin lesions) and two minor criteria (thrombophlebitis and cardiovascular lesions).

The first patient appears to be unique in having endocarditis involving the mitral and aortic valves. Because of the severe lung infection, this could be a bacterial or fungal endocarditis. No organisms were seen, however, and the swab taken postmortem was sterile. The morphological characteristics of the endocarditis were not typical for an infective aetiology. The vegetations were small, and a further unusual feature was the linear destruction of the ventricular aspect of the valve by the inflammatory process. This is the site where vegetations of systemic lupus erythematosus and other 'collagen' diseases sometimes occur. No fibrinoid necrosis was seen, and there was no evidence of previous rheumatic valvulitis. Davies⁹ described granulation tissue and chronic inflammatory infiltrate in the endocardium of the right ventricle with mural thrombosis in a patient with Behçet's disease, but no valvulitis has been reported in association with this condition. Buge *et al.*²⁰ described a patient with Behçet's disease who had massive endocardial fibrosis in the right ventricle with obliteration of the tricuspid valve. This could have been due to organisation of mural thrombosis secondary to valvulitis and endocarditis but there was no evidence of valvulitis at the time of necropsy. Clearly, further documentation of such cases is required to determine the progression of the condition. We conclude that the

Fig. 6 Case 2. Skin from punctate lesions on legs. There is mild spongiosis of the epidermis. The dermis shows capillaries with plump lining endothelium and a mild perivascular lymphocytic infiltrate. (Original magnification H and E $\times 300$).

endocarditis is probably due to Behçet's disease and may be a further manifestation of the systemic nature of this condition. The pathogenesis is unknown but is probably the same as that of the vasculitis which may have an immune basis. The changes seen on the mitral valve of the second patient, namely, endothelial cell swelling and lymphocytic infiltration, were similar to those in the cutaneous blood vessels. These vascular lesions have been noted by others in patients with Behçet's disease.^{9 21}

The fungal infection in the lungs was an opportunistic infection associated with the steroid therapy but pulmonary damage due to Behçet's disease may have preceded this. A 'honeycomb' pattern was seen on chest x-ray nine months before death and, although this was not seen at necropsy, the lungs were firm and 'gritty' on sectioning due to fibrosis of the septa and peribronchial tissue. Fibrosis of the lung occurs in patients with Behçet's disease,² and other pulmonary manifestations of Behçet's disease include vascular lesions with haemoptysis,⁹ fibrosis and inflammatory infiltrate,²² and pneumonitis.²³ Aphthous type ulcers of the bronchi also occur²⁴ and were present in our patient but with superimposed fungal infection. Hyaline membranes have not been described in Behçet's disease. Our patient was not in shock and did not have any of the conditions usually associated with the development of hyaline membranes in adults. This suggests that Behçet's disease may cause damage to the alveolar lining cells and result in the formation of hyaline membranes.

A third unusual feature of this patient is the haematological disturbance. This included relative lymphocytosis with atypical lymphocytes and splenomegaly early in the disease. Later, leucopenia developed and anaemia, associated with gross dyserythropoiesis and erythrophagocytosis in the bone marrow. Erythroid hyperplasia was present in the necropsy bone marrow. The changes may have an immune basis but since the aetiology of Behçet's disease is unknown, this is speculative. The peripheral blood in patients with Behçet's disease is either normal or shows transient leucocytosis during relapses¹ although a very occasional patient can have a lymphopenia.²⁵ The atypical cells seen in sections of the liver, spleen, lymph node, and stomach were strongly suggestive of lymphoma but the preservation of the tissue was too poor to allow accurate classification. Lymphoma has been described in patients with Behçet's disease²¹ and may have been the cause of the splenomegaly in our patient. It is possible that splenomegaly in a patient with Behçet's disease should raise the possibility of lymphoma. It has been described in isolated patients with other concurrent conditions¹³ but does not

seem to occur in uncomplicated Behçet's disease.

Involvement of salivary glands is also rare in Behçet's disease² although Sjögren's syndrome has been described.²⁶ The salivary gland enlargement in our patient was shown at necropsy to be due to necrosis and inflammation similar to that in the other Behçet's lesions. The changes are probably a manifestation of the disease itself, especially involving the duct epithelium.²⁷

Central nervous system lesions in Behçet's disease are well documented and were recently reviewed.² They include necrosis, demyelination, necrotising encephalitis, perivascular inflammatory infiltrate, and gliosis. The changes in our patient are non-specific.

Renal involvement is rare in this condition, but glomerulonephritis and amyloidosis have been described.² Only mild cortical scarring was seen in our patient, and the proteinuria present clinically was a terminal event and probably related to the cardiac failure.

In the second patient, the inferior vena cava, leg veins, and both renal veins were reduced to small, hard, solid cords with tiny recanalising channels. This organised thrombosis had obviously been present for some time. Despite occluded renal veins there was no evidence of renal damage. A similar situation has already been reported.²⁸ Thrombosis in many of the hepatic veins had been present for some time without causing symptoms, and the onset of hepatomegaly and hepatic failure was apparently due to recent thrombosis in previously uninvolved veins. The acute phase caused extensive liver cell necrosis and hepatic failure before ascites had time to develop. This unusual presentation has not been described previously. In three other cases of Budd-Chiari syndrome^{13 16 17} ascites was a prominent feature. The progression of the thrombosis in the hepatic veins in these patients appeared to be slow, as in our patient. In the patient described by Kansu *et al.*,¹³ the first liver biopsy showed only cholestasis, and signs of Budd-Chiari syndrome appeared in the second biopsy after a four-month interval. The first liver biopsy in the patient of Valleteau de Moulliac *et al.*¹⁶ showed only centrilobular congestion and did not show features of Budd-Chiari syndrome until the second biopsy three weeks later. Liver involvement in Behçet's disease is uncommon and asymptomatic¹ and does not appear to cause hepatomegaly except when associated with the Budd-Chiari syndrome. Features of liver disease in this condition should therefore raise the strong possibility of the Budd-Chiari syndrome, and therapy should be instituted as soon as this is confirmed. The slow progression of the thrombosis in these particular cases suggests that the process could be halted.

Although the prognosis of the Budd-Chiari syndrome is poor, one of the five cases reported (including the present case) survived after treatment with diuretics.¹⁶

Our second patient also had minor cardiac involvement in the form of focal myocardial cell degeneration and lymphocytic infiltrate and a scattering of lymphocytes and plump endothelial cells in the mitral valve. These could be related to the underlying Behçet's disease and may represent an earlier stage of the lesions seen in our first patient.

Skin lesions in Behçet's disease include various forms of vasculitis and erythema nodosum.² The cutaneous hypersensitivity so commonly described in this condition was not looked for clinically in this patient and is not always present.²¹ There was, however, cutaneous thrombophlebitis, perivasculitis, and endothelial cell swelling, the latter similar to that described by others.^{9, 21}

The cause of Behçet's disease is unknown but is thought to have an immune basis, possibly including B-cell mediated autoantibodies with depression of T cells²⁹ or an Arthus-type phenomenon involving immune complexes.³⁰ The various theories regarding aetiology have been reviewed recently.^{1, 31} The basic histopathological lesion appears to be a vasculitis,² and this is illustrated by the two patients reported here. These patients show that the endocardium can be affected in a similar manner to the blood vessels and that valvulitis should be added to the many manifestations of Behçet's disease.

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