Portal vein thrombosis despite anticoagulation in a person with diabetes

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J R Soc Med 2005;**98**:161–163

In a patient with unexplained fever and a potentially hypercoagulable state, a history of sore throat may be of crucial importance.

CASE HISTORY

A man aged 67 was admitted after six weeks of night sweats, rigors and fatigue. He complained of nausea but there had been no vomiting, abdominal pain or diarrhoea and currently he had no respiratory symptoms. The patient's daughter later revealed that she and her father had experienced mild sore throat and coryzal symptoms eight weeks earlier. The medical history included tuberculosis at age 21, an ischaemic stroke, type 2 diabetes mellitus diagnosed eighteen months ago and poorly controlled on diet (HbA_1C 9.0% on admission), congestive heart failure with paroxysmal atrial fibrillation, benign IgG (κ) paraproteinaemia diagnosed twenty-two months before admission, and stable chronic renal failure secondary to renal vascular disease (creatinine 300 μmol/L). His drugs on admission were amiodarone, gliclazide, furosemide, atorvastatin, spironolactone, and warfarin. His international normalized ratio (INR) had been 2.92 two months before admission and 3.48 two weeks before admission.

On examination he was apyrexial but sweaty, heart rate 95/min, blood pressure 140/80 mmHg; oxygen saturation was 96% on room air. He was noted to have very poor mouth and dental hygiene. Initial investigations showed haemoglobin 11.3 g/dL, white cell count 24.5×10^9/L (neutrophils 21.2), erythrocyte sedimentation rate 123 mm/h, C-reactive protein (CRP) 107 mg/L, INR 2.5, urea 18.9 mmol/L, creatinine 301 μmol/L, albumin 30 g/L, globulin 38 g/L, alkaline phosphatase 175 U/L, gamma-glutamyltransferase 180 U/L, glucose 14.3 mmol/L. On electrocardiography the only abnormality was long-standing first-degree atrioventricular block; the chest X-ray was reported as showing an enlarged heart with evidence of old tuberculosis. Blood and urine cultures taken over the next 4 days were negative. An echocardiogram showed mild impairment of left ventricular function but nothing else abnormal. While he was in hospital his temperature rose to 39.4°C, but no antibiotics were given because no source of infection was identified. The leukocyte count remained high at 24.1×10^9/L and his CRP rose to 130 mg/L. A haematology review (requested because of the benign paraproteinaemia) was unrewarding, and an autoantibody screen for collagen vascular disease was negative. There was no evidence of paroxysmal nocturnal haemoglobinuria, and levels of protein S and factor V Leiden were normal. Protein C levels were not determined because the patient was on warfarin. IgM and IgG anticardiolipin antibody levels were within normal limits. Antithrombin concentrations were normal. We did not investigate the possibility of a mutation in the prothrombin gene. CT of the abdomen and pelvis suggested the presence of a cholangiocarcinoma with tumour or thrombus within the portal vein. Subsequent MRI confirmed extensive portal venous thrombosis but showed no evidence of a cholangiocarcinoma.

During a rigor twelve days after admission another set of blood cultures was taken, and these grew anaerobic Gram-negative bacilli identified as *Fusobacterium nucleatum*. The bacterium was sensitive to clindamycin, metronidazole and cefotaxime. On intravenous clindamycin 600 mg three times daily the patient swiftly lost all his symptoms. He was discharged on long-term warfarin.

COMMENT

F. nucleatum has most often been associated with internal jugular venous thrombosis, initially described by Lemierre in 1936.[1] To our knowledge, only five cases of portal vein thrombosis with *F. nucleatum* or *F. necrophorum* have been reported (Table 1).[2–6]

This case is unusual for two reasons. First, the portal vein thrombosis developed despite good anticoagulation. Second, the patient had diabetes. In two of the previous cases the patients had experienced pharyngitis in the weeks beforehand and the bacterium was presumed to have gained entry via the oropharynx;[3,6] in the other three the gastrointestinal tract was judged the likely route.[2,4,5] We assume that our patient's history of sore throat was relevant, though we disovered this only late in the course of his illness, when we quizzed his daughter closely

How might *Fusobacterium* spp. predispose to thrombosis? One suggested mechanism is thrombogenesis by the lipid A component of the bacterial lipopolysaccharide endotoxin; another is the binding of *Fusobacterium* to human plasminogen, activating local proteolysis and tissue

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Table 1 **Summary of published case reports for portal vein thrombosis associated with *Fusobacterium* infection**

Clinical features	***Soo* et al. *[2]***	***Bultink* et al. *[3]***	***Etienne* et al. *[4]***	***El Braks* et al. *[6]***	***Verna* et al. *[5]***
Age/sex	31 / M	23 / M	68 / M	71 / F	56 / M
Medical history	None reported	None reported	Lung and genitourinary tract tuberculosis, thrombocytopenia, recurrent pulmonary emboli, inferior vena cava filter	Surgically corrected urinary incontinence	Ulcerative colitis of rectosigmoid
Symptoms and signs	Fever, rigors abdominal pain, diarrhoea, vomiting for 14 days, upper abdominal pain, jaundice	Fever, rigors abdominal pain, vomiting for 14 days, hepatosplenomegaly, pleuropericarditis	Fever, lung base crackles for 3 days	Fever and severe epigastric pain for 1 day	Fever, chills, anorexia, jaundice for 8 days
Oropharyngeal infection	Not reported	Yes (5 weeks before presentation)	No	Yes (pharyngitis on examination)	No
Other recognizable portal of entry	GI tract	No	GI tract (uncomplicated colonic diverticulosis)	No	GI tract (ulcerative colitis)
Laboratory findings	Leukocytosis, mild LFT abnormalities	Leukocytosis with left shift, abnormal LFTs	Leukopenia, idiopathic CD4 lymphopenia, high CRP, mild LFT abnormalities	Leukocytosis with left shift, abnormal LFTs, increased CRP, negative autoimmune markers	Mild leukocytosis and LFT abnormalities, raised factor VIII
Positive specimen cultures	Yes—blood	Yes—blood (5 out of 14 samples after 7 to 10 days)	Yes—blood (3 out of 3 samples after 7 days)	Yes—mesenteric node culture	Yes
Imaging studies and results	U/S, MRI: superior mesenteric and portal vein thrombosis	U/S, CT abdomen: portal vein thrombosis, hepatosplenomegaly	U/S: liver abscess CT abdomen: liver abscess, portal vein thrombosis TOE, WBC scan (both negative)	U/S, CT abdomen: portal and superior mesenteric vein Thrombosis	U/S abdomen and ERCP (both negative) CT abdomen: left portal vein thrombosis
Antibiotic therapy	IV ciprofloxacin for 4 days, then IV metronidazole and penicillin. Oral amoxicillin/ clavulanate and metronidazole for 6 weeks	IV penicillin 6 weeks	IV cefotaxime 1 week; IV metronidazole, then oral metronidazole 2 weeks after day 24	IV piperacillin–tazobactam 2 weeks; then ofloxacin 3 weeks	IV clindamycin 2 weeks
Anticoagulation therapy	IV heparin followed by warfarin 6 months	A few days of heparin	Prophylactic enoxaparin 24 days	IV heparin initially, then 9 months of oral fluindione	None
Outcome	Survival	Survival with persistent portal vein thrombosis	Survival	Survival with partial resolution of portal vein thrombosis; complete resolution of mesenteric vein thrombosis	Survival with persistent of portal vein thrombosis

GI, gastrointestinal; LFT, liver function tests; CRP, C-reactive protein; U/S, ultrasound scan; TOE, transoesophageal echocardiogram; WBC, white blood cell; ERCP, endoscopic retrograde cholangiopancreaticogram; IV, intravenous; MRI, magnetic resonance imaging

damage.[3,4] Our patient was well anticoagulated with warfarin and his clotting markers were normal; however, he did have two hypercoagulability factors—namely, diabetes[7] and a paraproteinaemia.[8] We conclude that, in a patient such as this with unexplained fever and abdominal symptoms, a history of upper respiratory tract infection should be sought and blood cultures should be taken to detect this fastidious anaerobic organism.

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Perindopril and pulmonary eosinophilic syndrome

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J R Soc Med 2005;**98**:163–165

Angiotensin converting enzyme (ACE) inhibitors are responsible for several respiratory effects including cough and angioneurotic oedema but an association with pulmonary eosinophilic syndrome is uncommon.

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CASE HISTORY

A Caucasian woman aged 68 was seen after two weeks of malaise, nausea and sinusitis, for which she had been prescribed clarithromycin. Seven weeks earlier she had been started on perindopril for hypertension, at which time a full blood count was normal. She was also taking co-amilofruse and was using inhaled medications for asthma—fluticasone, begun eighteen months earlier to replace the oral prednisolone she had taken for 15 years, and salbutamol. There was no travel history of note and she kept no household pets. On examination she was apyrexial. No abnormal physical signs were detected—in particular no rash or subcutaneous nodules. Blood pressure was 109/80 mmHg and oxygen saturation 97% on air. Haemoglobin was 10.1 g/dL, MCV 93fL, neutrophils 9.9×10^9/L and the eosinophil count was 13.4×10^9/L (52%). Platelet count and clotting studies were normal; sodium was 128 mmol/L, potassium 4.8 mmol/L, urea 4.5 mmol/L, creatinine 58 μmol/L, albumin 31 g/L, corrected calcium 2.38 mmol/L, C-reactive protein 86 mg/L. There was no active urinary sediment. On sinus radiography the ethmoid and maxillary sinuses were opaque. A chest radiograph showed hyperinflated lungs and a small area of pleural scarring at the left costophrenic angle.

On admission to hospital, perindopril, clarithromycin and the diuretic were withdrawn, and she was continued on a fluticasone inhaler. A low-grade pyrexia developed and on day 6 the eosinophil count had risen to 18.3×10^9/L (61%). CT revealed pulmonary infiltrates with mediastinal lymphadenopathy but no proximal bronchiectasis (Figure 1). Further investigations showed aspergillus precipitins weakly positive at titre 1:2, IgE 576 kU/L (normal 0–81), stool examination negative for ova, cysts and parasites, and

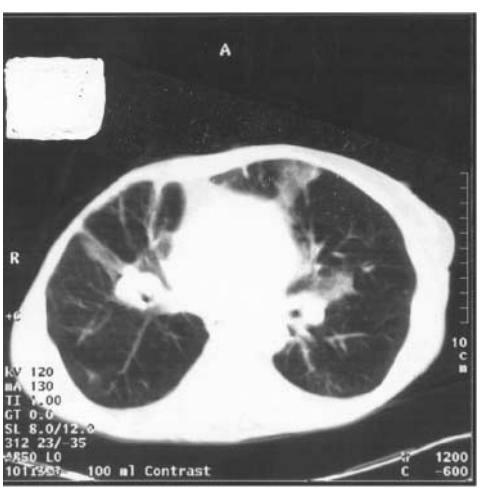

Figure 1 **CT of thorax showing prominent peripheral infiltrates in the anterior segments of upper lobes and precarinal lymphadenopathy, an opacity at the right apex and bilateral pleural effusions**