Unusual association of diseases/symptoms

Adenocarcinoma of lung masquerading as systemic auto-immune disease

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Summary

A 40-year-old previously healthy male presented with acute onset painless dimness of vision in both eyes since the past week and low-grade fever, anorexia and weight loss for the past 1 month. He had been evaluated at a local hospital and diagnosed to have a posterior cerebral artery territory infarct on the left side on the strength of cranial CT. Shortly after receiving antiplatelets and warfarin he had developed severe coagulopathy as evidenced by haematemesis, epistaxis and haematuria. Preliminary investigation revealed prolonged clotting parameters, renal failure and anaemia. Cerebral MRI showed multiple areas of cortical haemorrhage. In the course of his hospital stay, he developed further stigmata of auto-immunity including Coomb's positive haemolytic anaemia, recurrent venous thromboses and a palpable purpuric truncal rash. He was eventually diagnosed to have an adenocarcinoma of the lung, and was subsequently referred to an oncologist for further therapy.

BACKGROUND

This case highlights the remarkable propensity of neoplasms to mimic systemic auto-immune diseases, a situation that can result in potentially disastrous consequences for the misdiagnosed patient. Conversely, recognition of the possibility of underlying cancer can lead to an early diagnosis of neoplastic disease in these patients. As our report amply demonstrates, such manifestations can often antedate symptoms arising from local effects of tumour growth, providing an opportunity for rapid initiation of appropriate therapy. Physicians attending to patients with suspected systemic auto-immune disorders and vasculitides need to be vigilant regarding the possibility of occult malignancy, even in patients at lower risk such as our own case.

CASE PRESENTATION

A 40-year-old previously healthy male, presented with sudden onset painless dimness of vision in both eyes since the past week. In addition, he had noticed low-grade fever,

anorexia and weight loss for the past 1 month, although he had not attributed importance to these symptoms. He had been evaluated at a local hospital and diagnosed to have a posterior cerebral artery territory infarct on the left side on the strength of cranial CT. He was therefore treated with aspirin 75 mg PO OD and warfarin. Shortly after, the patient developed features of severe coagulopathy including recurrent bouts of haematemesis, epistaxis and episodic haematuria. He was immediately referred to us for further management. There was no history of substance abuse in the past and the patient also denied any episodes of unprotected sexual exposure.

At presentation, the patient was in shock with a systolic blood pressure of 80 mm Hg. General examination also revealed moderate pallor, and multiple ecchymoses over his trunk. There was no significant lymphadenopathy or organomegaly. Neurologic examination showed a right homonymous haemianopia but was otherwise normal. In the course of hospital stay, he would also develop a palpable purpuric truncal rash.

Figure 1 Cranial CT, axial section showing left occipital infarct (thick black arrow, A). Cranial CT, sagittal section showing multiple haemorrhagic foci (thin black arrows, B). Cerebral MRI, sagittal section, T1 sequence, showing multiple well-defined cortical based haemorrhages (white arrows, C).

Figure 2 Thoracic radiogram showing left parahilar mass (black arrow, A). CT thorax showing a heterogeneously enhancing mass with amorphous calcifications and spiculated margins in the left hilar region mass causing abrupt cut of the left upper lobe bronchus, with interstitial thickening (white arrows, B, C).

INVESTIGATIONS

Preliminary investigations revealed anaemia (Hb: 7.9 g/dl), elevated erythrocyte sedimentation rate (59 mm/h) and renal failure (serum creatinine: 5.5 mg/dl). Clotting parameters were grossly deranged (prothrombin time: 77 s, international normalised ratio: 5.92; activated partial thromboplastin time >120 s). Platelet count (353 000/mm³) and bleeding time (3 min) were normal. Peripheral blood smear showed normocytic and normochromic erythrocyte morphology. Direct Coomb's test was positive. Urine tested positive for haemoglobin, and numerous red cells were seen on microscopy. Stool was also positive for occult blood, microscopy showed occasional red cells. Cranial CT imaging showed left occipital lobe infarct (figure 1A) as well as multiple well-defined cortical lesions suggestive of acute haemorrhage (figure 1B). Cerebral MRI was confirmatory (figure 1C). Blood and urine cultures were persistently sterile. Venous Doppler studies performed after the patient developed acute severe pain in his legs, demonstrated subacute thrombosis in his right leg. An inferior vena cava (IVC) filter was then placed by cardiologists. Subsequently, the patient developed another deep vein thrombosis in his left leg. Trans-thoracic echocardiography ruled out any vegetation. Screening for auto-immune markers including antinuclear antibodies, antineutrophil cytoplasm antibodies, antiphospholipid antibodies was negative. Flow-cytometry for CD-55 and CD-59 positivity ruled out paroxysmal nocturnal haematuria. Oesophagogastrosocopy revealed a solitary oesophageal ulcer. Biopsy was initially deferred in view of the coagulopathy. A second endoscopy performed after correction of clotting parameters with fresh frozen plasma confirmed that the ulcer had healed. Careful review of serial thoracic radiograms revealed a non-resolving left parahilar shadow (figure 2A) which had been assumed previously to be consolidation following aspiration. CT imaging of his chest and abdomen was done. A heterogeneously enhancing mass with amorphous calcifications and spiculated margins was seen in the left hilar region (figure 2B,C), causing abrupt cut off of the left upper lobe bronchus and interstitial thickening suggestive of lymphangitic spread, along with mediastinal lymphadenopathy. A thrombus was also visualised within the inferior vena cava extending into the common iliac veins. Fibre-optic bronchoscopy demonstrated a pearly white growth occluding the apico-posterior segment of the left upper lobe. Biopsy of the mass showed an infiltrating

moderately differentiated adenocarcinoma (figure 3A,B) with severe cytologic atypia and mixed solid and acinar architecture. Staging of the tumour according to the TNM classification was IIIA (T2aN2M0).

DIFFERENTIAL DIAGNOSIS

- Adenocarcinoma of lung with cerebral metastases/cerebral haemorrhage secondary to coagulopathy, recurrent deep vein thrombosis and autoimmune haemolytic anaemia, suspected secondary glomerulonephritis with renal failure.
- Connective tissue disease with multi-system involvement, possible antiphospholipid syndrome and autoimmune haemolytic anaemia.
- Subacute endocarditis with haemorrhagic septic emboli and secondary glomerulonephritis with renal failure.

TREATMENT

The patient was treated initially with supportive therapy including transfusions of fresh frozen plasma and multiple sessions of haemodialysis. Following the development of deep vein thrombosis in his right leg, an IVC filter was inserted by cardiologists. Subsequently, however, the patient developed deep vein thrombosis in his left leg, and was started on low-dose heparin infusion with close monitoring of activated partial thromboplastin time. The patient was also administered multiple analgesics including paracetamol, tramadol, dextropropoxyphene and finally morphine for severe pain in his legs. Non-steroidal anti-inflammatory drugs were avoided in view of renal failure and coagulopathy.

OUTCOME AND FOLLOW-UP

Improvement was noted after supportive therapy in the form of resolution of haemorrhagic tendency and partial relief of lower limb pain. Renal failure recovered completely over a period of 3 weeks after admission, at which point haemodialysis was stopped. The patient was subsequently referred to an oncologist for management of adenocarcinoma of lung.

DISCUSSION

Paraneoplastic syndromes comprise a diverse group of disorders resulting from indirect or remote effects of neoplastic disease, and not as a result of direct invasion or

Figure 3 Photomicrograph of biopsy showing glandular structure with infiltrating carcinomatous cells and desmoplasia at magnifications of 25X, 40X and 100X respectively, H&E stain (A–C).

metastasis. These syndromes can be classified broadly into neurologic disease, haematologic disease, vasculitides and other miscellaneous conditions including musculo-skeletal disease. Paraneoplastic manifestations often occur early in the natural history of cancer, prompting suggestions that they might be useful as early markers of disease.¹ Needless to say, such supposition is contingent on the treating physician recognising them as such, and then carefully searching for underlying occult tumour. The low index of suspicion in daily practice is emphasised by a review¹ of patients with non-small cell lung carcinoma where over half the patients (36 of 68 cases) were diagnosed on the strength of thoracic radiograms ordered for tumour-unrelated symptoms.

Our case is extremely interesting because of the number and variety of paraneoplastic manifestations observed simultaneously. In the course of his illness, the patient displayed features of renal and cutaneous vasculitis, auto-immune haemolytic anaemia and antiphospholipid antibody syndrome.

Paraneoplastic vasculitides have been described in association with a range of neoplasms,² including solid tumours and haematologic malignancies. A retrospective study³ of 60 patients with paraneoplastic vasculitis showed underlying adenocarcinoma of lung in three cases. Overall, the commonest form of vasculitis encountered was a small-vessel leukocytoclastic vasculitis. Pertinent to this observation is the reported association of Henoch–Schönlein purpura with malignancy.⁴ While a renal biopsy could not be performed in our patient owing to concurrent coagulopathy, the clinical pattern of palpable purpura over the lower limbs and renal involvement strongly favoured a diagnosis of Henoch–Schönlein purpura.

Antiphospholipid antibody syndrome is another recognised paraneoplastic manifestation, characterised by recurrent thrombotic episodes and a prolonged activated partial thromboplastin time. Both these features were also observed in our patient although tests for anticardiolipin antibodies and dilute Russell viper venom test were negative.

The third paraneoplastic phenomenon seen in this case, that is, immune hemolytic anemia is relatively uncommon in the setting of solid tumours; instead, it is a notable complication of haematologic malignancy, especially chronic lymphocytic leukemia. Before labelling it as an

auto-immune phenomenon, other causes of immune haemolytic anaemias should of course be excluded; chiefly, drug-induced immune haemolytic anaemia. In our patient, this possibility was ruled out as the patient denied receiving any drugs known to cause immune haemolytic anaemia, before conducting the direct Coombs' test.

In conclusion, while paraneoplastic auto-immune phenomena are well documented in medical literature,⁵ our case demonstrates an unusual and previously unreported convergence of three auto-immune syndromes with distinctly different pathogenetic mechanisms in the same patient. Diagnosis of the underlying clinically silent malignancy permitted referral to an oncologist while in Stage IIIA – potentially curable disease.

Learning points

- ▶ A wide spectrum of auto-immune phenomena can occur in patients with neoplastic disease.
- ▶ Multiple auto-immune manifestations can occur simultaneously in these patients.
- ▶ Careful clinical screening for malignancy in these patients with targeted investigations can result in early diagnosis; conversely, misdiagnosis can delay antineoplastic therapy, adversely impacting the patient's chances of survival.

Competing interests None.

Patient consent Obtained.

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