TUBERCULOSIS AND INVASIVE PULMONARY ASPERGILLOSIS IN A YOUNG WOMAN WITH A MYELODYSPLASTIC SYNDROME

Y K Kueh, S B Chionh, T Y Ti, W C Tan, Y S Lee

ABSTRACT

A 29-year-old Chinese woman developed pyrexia, multiple skin abscesses and bilateral fine nodular lung infiltrates about 3 months after the commencement of therapy for idiopathic thrombocytopenic purpura (ITP). Pseudomonas aeroginosa was isolated from the abscesses but multiple blood and sputum cultures, as well as a broncho-alveolar lavage did not yield any microorganisms. The persistence of fever and pulmonary infiltrates warranted an open lung biopsy which provided a definitive diagnosis of tuberculous-aspergillus granulomatous lung disease. Bone marrow re-examination revised the primary haematological disorder to that of a trisomy 8 associated myelodysplastic syndrome.

Keywords: nodular lung infiltrates, tuberculous-aspergillus granulomas, myelodysplastic syndrome

SINGAPORE MED J 1995; Vol 36: 107-109

INTRODUCTION

Recurrent bacterial infections are common in patients with the myelodysplastic syndrome because of the frequent association with significant neutropenia. An adequate granulocyte level may not prevent infections because impaired neutrophil functions are a prominent feature of the syndrome. Granulocytic dysfunction may be further compounded by therapy-related causes.

We report on a 29-year-old Chinese woman who developed bacterial infections of the skin and tuberculous-aspergillus granulomatous lung disease while receiving treatment for thrombocytopenia presumed to be due to idiopathic thrombocytopenic purpura (ITP). Re-investigation revealed that her primary disorder was a trisomy 8-associated myelodysplastic syndrome.

CASE REPORT

WS, a 29-year-old Chinese Indonesian housewife from Java, presented to us in May 1991 after having failed three and a half months of therapy for a presumed diagnosis of chronic ITP. Her diagnosis was based on the symptoms of easy bruising and a reduced platelet count in the face of normal bone marrow megakaryocytes. The presence of antiplatelet antibody and marrow cytogenetic abnormalities were not determined as these examinations were not available where she came from.

The three-and-a-half month therapy had consisted of an initial six weeks of oral prednisolone (45 mg daily) and a further eight weeks of oral methylprednisolone (20 mg daily) together with 6-mercaptopurine (100 mg daily). There was no improvement in her platelet counts or purpura. In the first week of May she developed fever and later, multiple skin pustules. She was hospitalised in her hometown and given oral cloxacillin. The methylprednisolone and 6-mercaptopurine were discontinued and she was given oral prednisolone 30 mg daily. Her fever persisted, the skin pustules developed into abscesses and she experienced recurrent epistaxis. Her family brought her to Singapore in the middle of May, 1991.

On arrival she was desperately ill. She was febrile and pale. Nasal packing was carried out immediately to stop the profuse epistaxis. Large and small ecchymoses and multiple abscesses were present on her extremities and trunk. Her right maxilla was inflamed and tender to touch. Clinically the lungs and heart were normal. The liver was mildly enlarged and could be felt 3 cm below the right costal margin. The spleen and lymph nodes were not enlarged. The neurological examination including fundoscopy was normal.

Investigations revealed severe thrombocytopenia (platelets 16 X 10^9 / l) and anaemia (haemoglobin 7.2 g/dl). The WBC was 5.59 X 10^9 /l with a normal differential count. The reticulocyte count was 2.2% and direct Coombs' test was negative. The peripheral blood film showed mildly macrocytic erythrocytes without changes to suggest microangiopathic haemolysis. The Ham's test was negative. Antiplatelet antibody was not detected in the serum. The antinuclear antibody fluorescence test was weakly positive but the anti-double-stranded DNA antibody level was not raised. Dyshaemopoiesis including the presence of micromegakaryocytes was seen in the bone marrow in association with a trisomy 8 karyotype in over 90% of dividing marrow cells. This altered the primary diagnosis to that of a myelodysplastic syndrome.

The total bilirubin was not elevated but the hepatic enzymes were mildly to moderately raised: gamma glutamyl transferase 237 u/l (normal 5-80), alanine transaminase 228 u/l (normal 5-56), aspartate transaminase 67 u/l (normal 5-40), alkaline phosphatase 188 u/l (normal 38-126) and lactate dehydrogenase 1230 u/l (normal 300-650). There was a polyclonal elevation of the serum immunoglobulins. Cultures of urine, blood and sputum

Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

Y K Kueh, FRCP
Associate Professor

W C Tan, MD, FRACP, FCCP, FRCP(Edin)
Professor

Y S Lee, MD, FRCPA, FCAP
Professor

S B Chionh, MRCP(UK)
Former Resident

Department of Pharmacology
National University of Singapore
Kent Ridge Crescent
Singapore 0511

T Y Ti, FRCP
Associate Professor

Correspondence to: Dr Y K Kueh

were negative for microorganisms. Acid fast bacilli were not seen in the sputum. Pus aspirated from several skin abscesses gave a heavy growth of *Pseudomonas aeroginosa* sensitive to gentamicin. The chest radiograph and computerised tomographic (CT) scan both showed bilateral fine nodular infiltrates (Fig 1a and b). A CT scan of the face showed mucosal thickening of the right maxillary and ethmoidal sinuses with no bony erosion or localised fluid collection. An abdominal ultrasound scan revealed an enlarged liver with diffusely increased echogenicity but no focal lesions.

Fig 1a – Chest radiograph with bilateral nodular lung infiltrates.

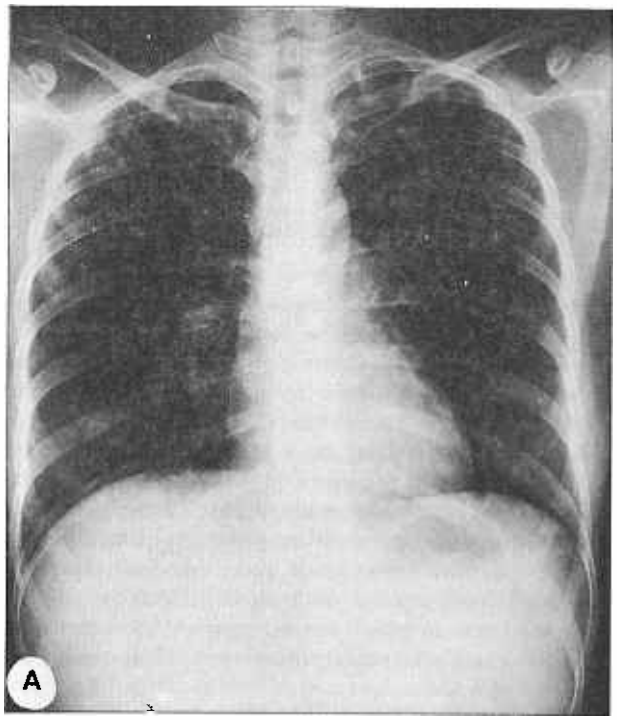
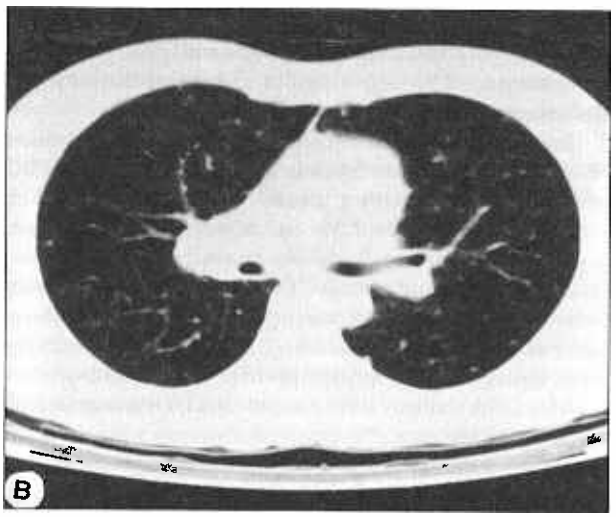


Fig 1b – Computerised tomograph with bilateral nodular lung infiltrates.



In view of the preceding months of immunosuppressive therapy and the progression of the skin pustules to frank abscesses despite oral cloxacillin, the patient was prescribed a combination of gentamicin, ceftazidime and vancomycin. The abscesses and the inflamed right cheek resolved rapidly but the fever persisted. A bronchoalveolar lavage showed no *Pneumocystis carinii*, acid fast bacilli or malignant cells in the bronchial washings. Fungal and mycobacterial cultures were negative. Serum mycoplasma and legionella antibody titres were not raised. Recultures of blood and urine were sterile. An open lung biopsy was arranged.

At thoracotomy the right lung surface was discovered to be studded with numerous 5 mm hard nodules, some being adherent to the pleura. A wedge lung biopsy was obtained. Sections of the lung biopsy showed both caseating and non-caseating granulomas. Acid fast bacilli were identified in the former and large numbers of fungal hyphae, with features consistent with the Aspergillus species in the latter (Fig 2a-d). Mycobacterium tuberculosis and Aspergillus fumigatus were confirmed by culture.

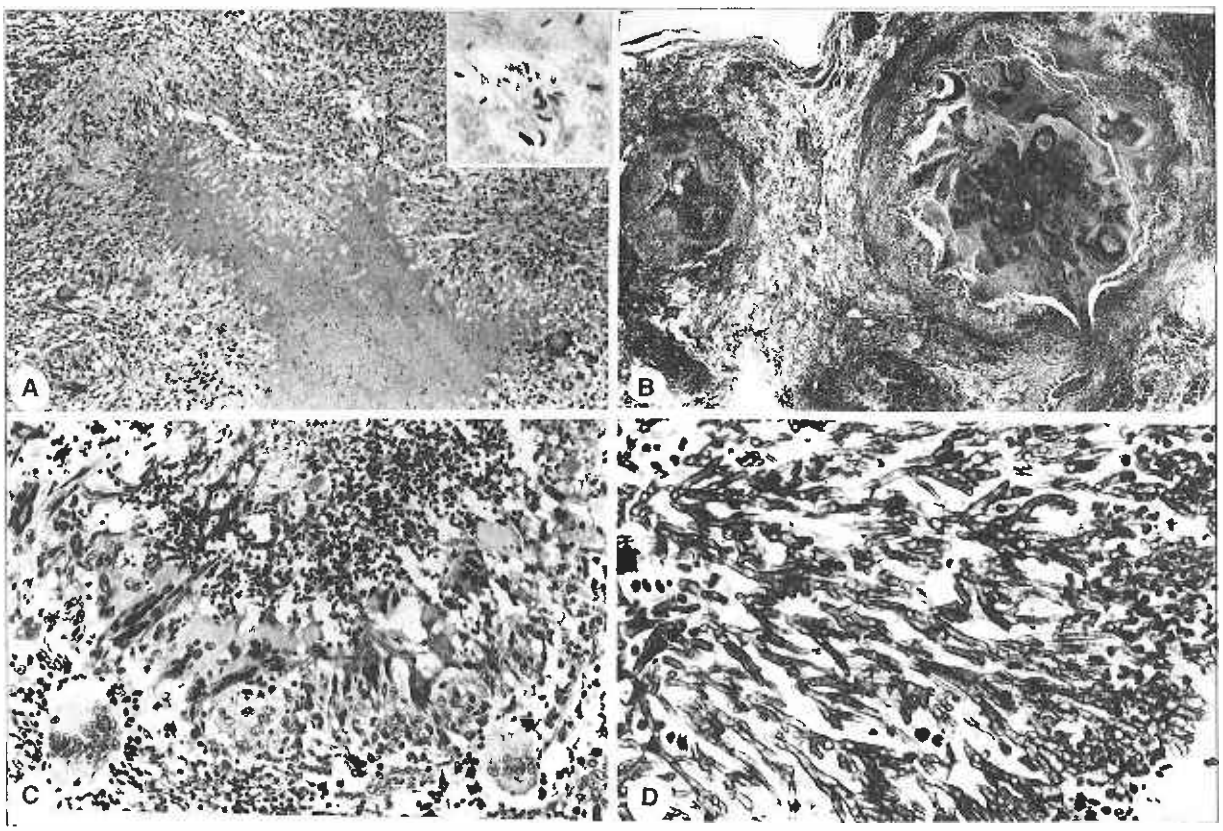
The patient was successfully treated with amphotericin B and triple-drug (isoniazid, rifampicin and ethambutol) antituberculous therapy. At the time of reporting she is well but has a persistent thrombocytopenia due to her underlying myelodysplastic syndrome.

DISCUSSION

The diagnosis of chronic ITP is generally based on the exclusion of disorders and situations known to be associated with reduced blood platelets[1]. The diagnosis is often tentative when unsupported by the presence of antiplatelet antibody. The facility for antiplatelet antibody detection is not widely available in this region. Bone marrow cytogenetic analysis is even more restricted and is not normally performed because myelodysplasia is an uncommon cause of thrombocytopenia in young adults. The atypical clinical course of our patient cast doubt on the diagnosis of ITP and a re-examination uncovered a trisomy 8 myelodysplastic syndrome.

Defective neutrophil functions such as impaired phagocytosis and chemotaxis have been described for various subsets of the myelodysplastic syndromes including that associated with a trisomy 8 bone marrow karyotype[2-4]. A common complication experienced by a patient with a myelodysplastic syndrome is recurrent bacterial infections[5]. Invasive aspergillosis is typically described in the clinical setting of protracted, treatment-induced, severe neutropenia[6]. But since abnormal phagocytic function is the single most important predisposing factor to this opportunistic infection[7], it may occur in the absence of neutropenia if phagocytic dysfunction is profound. The prolonged supraphysiological doses of corticosteroid preparations our patient received predisposed her to tuberculosis and invasive aspergillosis. The plethora of infections our patient experienced is a strong reminder of the hazards of therapy-aggravated immunocompromise.

Fig 2 – A caseating granuloma (a) with acid fast bacilli in the inset and non-caseating granulomas containing fungal hyphae (b) with dichotomous branching and septae (c and d) characteristic of the Aspergillus species.



ACKNOWLEDGEMENT

We thank Mr SL Fung for preparing the photoprints and Ms Jessie Lim for typing the manuscript.

REFERENCES

1. McMillan R. Chronic idiopathic thrombocytopenic purpura. N Engl J Med 1981; 304:1135-48.
2. Boogaerts MA, Nelissen V, Roelant C, Goosens W. Blood neutrophil function in primary myelodysplastic syndromes. Br J Haematol 1983; 55:217-27.
3. Ruutu P. Granulocyte function in myelodysplastic syndromes. Scand J Haematol 1986; 36 (Suppl 45):66-70.
4. Ruutu P, Ruutu T, Vuopio P, Kosunen TU, de la Chapelle A. Function of neutrophils in preleukemia. Scand J Haematol 1977; 18:317-25.
5. Martin S, Baldock SC, Ghoneim AIM, Child JA. Defective neutrophil function and microbicidal mechanisms in the myelodysplastic disorders. J Clin Pathol 1983; 36:1120-8.
6. Anaissie E. Opportunistic mycosis in the immunocompromised host: experience at a cancer center and review. Clin Inf Dis 1992; 14 (Suppl 1): S43-53.
7. Levitz SM. Overview of host defenses in fungal infections. Clin Inf Dis 1992; 14 (Suppl 1): S37-42.