Postgraduate Medical Journal (August 1983) **59**, 508–511

Occult pulmonary thromboembolism presenting as diffuse interstitial pneumonitis in cancer patients

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Summary

The prompt and accurate recognition of non-malignant complications is of critical importance in the care of cancer patients. Pulmonary thromboembolism is particularly important because it is common, treatable and frequently difficult to diagnose. Two patients are presented who died of recurrent pulmonary thromboemboli which were unrecognized because open lung biopsies showed diffuse interstitial pneumonitis. The association of pulmonary thromboembolism and interstitial inflammation has been recognized at autopsy, and there are a number of plausible mechanisms which could link these processes. Interstitial pneumonitis should be added to the numerous protean manifestations with which pulmonary thromboembolism is associated.

KEY WORDS: pulmonary embolism, diffuse interstitial pneumonitis, inflammation, thrombosis, cancer chemotherapy.

Introduction

Diffuse interstitial pneumonitis can acutely complicate the course of patients with a variety of neoplasms. Numerous aetiologies have been reported including fungal infection (Fisher and Armstrong, 1977), *Pneumocystis carinii,* cytomegalovirus and other viral infections (Singer *et al.,* 1979), radiation therapy (Wara, Phillips and Margolis, 1973), hypersensitivity to a variety of anti-neoplastic agents such as bleomycin (Whitcomb, 1973), and graft-versus-host disease (Graze and Gale, 1979). Pulmonary thromboembolism has been reported to be associated with prominent interstitial fibrosis at autopsy (Saldeen, 1979), but this association is not clinically recognized. We have recently observed 2 cases of interstitial pneumonitis in patients with cancer in whom we feel occult, underlying pulmonary thromboembolism was the aetiology.

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Case reports

Case 1

A 65-year-old Caucasian female presented complaining of weakness. Physical examination disclosed a large abdominal mass. Laboratory investigation revealed an autoimmune haemolytic anaemia. Prednisone was begun, with improvement of the anaemia, and she was admitted to the hospital for laparotomy. At this procedure, an extensive retroperitoneal malignancy was demonstrated, and biopsy of lymph nodes led to the diagnosis of diffuse histiocytic lymphoma. Her post-operative course was uneventful and she was subsequently begun on combination chemotherapy comprising cyclophosphamide, adriamycin, vincristine and prednisone.

During the second chemotherapy cycle, she complained of fever, weakness, dyspnoea and productive cough and she was readmitted to the hospital. On examination, she was febrile and the chest was clear. The Po_2 on room air was 53 mmHg, while the Pco_2 was 26 mmHg and pH 7·53. Chest X-ray initially revealed interstitial infiltrates of the left upper lobe which rapidly progressed to involve all lung fields. Diffuse dry rales became audible. Fever persisted despite cephalosporin therapy. Cultures of blood, urine and sputum were negative.

Fibreoptic bronchoscopy was performed and revealed an inflamed tracheobronchial tree. A transbronchial lung biopsy revealed interstitial inflammation and fibrosis. She subsequently developed ventilatory failure. An open lung biopsy was performed

0032-5473/83/0800-0508 $02.00

and demonstrated interstitial pneumonitis. Corticosteroids in high doses and antituberculous therapy were begun. Her oxygen tension stabilized and she was discharged. Fever and dyspnoea recurred however, and several weeks later she developed an acute dyspnoeic episode and died.

At autopsy, the left lung exhibited an apical abscess, 3·5 cm in diameter; numerous wedge-shaped organized infarcts were scattered throughout both lungs. The right and left main pulmonary arteries were occluded by recent antemortem thromboemboli. On microscopic examination, there were diffuse interstitial inflammatory changes and fibrosis. Numerous small arteries and arterioles were occluded with emboli, although in the most peripheral vessels they were less prominent. Thrombi were found in the thigh veins bilaterally. Post-mortem lung and blood cultures were negative.

Case 2

A 34-year-old Caucasian female presented with a 48-hr history of easy bruising, gross haematuria and malaise. Circulating leukaemic cells were observed and she was referred for further evaluation.

The white cell count was elevated at $18{\cdot}0\times10^9$/litre with 14×10^9/litre blasts and $0{\cdot}72\times10^9$/litre segmented neutrophils. Haemoglobin was 9 g/dl with normal erythrocyte indices. The platelets were decreased at 5×10^9/litre. The fibrinogen was 82 mg/dl and the prothrombin time was prolonged to 17/s. Fibrin degradation products were markedly elevated. Marrow examination revealed a hypercellular marrow packed with myeloblasts and promyelocytes, with occasional auer rods. Remission induction was attempted with thioguanine, cytarabine, daunomycin, vincristine and prednisone. Heparin and cryoprecipitate were administered for the coagulopathy.

On the fourth hospital day, fever, acute dyspnoea, hypoxaemia, tachycardia, tachypnoea, diffuse rales and pulmonary infiltrates (Fig. 1) were noted. Antibiotics were begun, heparin continued, and the respiratory distress abruptly resolved. Laboratory evidence of disseminated intravascular coagulation (DIC) responded to heparin administration. Similar episodes occurred on the 12th, 13th, 18th and 20th days. Trimethoprim-sulphamethoxazole was added, but the fever persisted. On the 23rd day, an open lung biopsy was performed and revealed alveolar septal fibrosis, reactive proliferation of alveolar pneumocytes, and residual proteinaceous debris in alveoli and small bronchioles. Inflammatory cells were evident in the alveolar septae. Special stains for bacteria, mycobacteria, and fungi were negative, as were viral cultures and direct tissue immunofluorescence for Legionella. The small arteries and veins were devoid of thrombi.

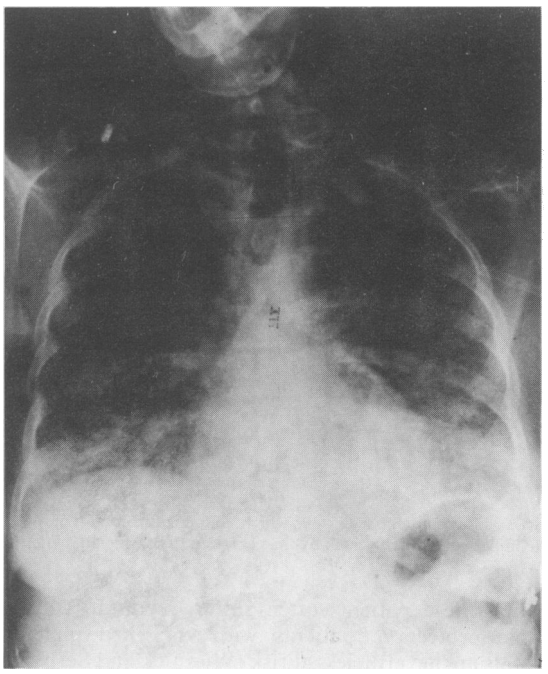

FIG. 1. Chest X-ray, P/A projection, Case 2, 4th hospital day. Diffuse patchy interstitial infiltrates are noted.

Subsequently, the patient suffered acute renal failure, a second central nervous system haemorrhage, cardiopulmonary arrest, and died on the 30th hospital day. At autopsy, the lungs had a nodular appearance produced by firm, raised, deep red infarcts scattered through the parenchyma. The infarcts were associated with visible, often friable thrombi in medium and large vessels and were predominantly central, rather than in the classic subpleural location. On microscopic examination, most of the lung tissue appeared similar to the biopsy specimen and was similarly devoid of visible bacteria, mycobacteria, and fungi. Centrally, however, there were numerous pulmonary infarcts, associated with arterial and venous thrombi which consisted of masses of fibrin and fungal hyphae. Special stains demonstrated vascular mural invasion by fungi in occasional large vessels (Fig. 2).

Discussion

Pulmonary embolism is a highly treatable disease with protean manifestations. If unrecognized, the outcome can frequently be fatal. Pulmonary thromboembolism complicates the course of cancer patients frequently. Although thrombocytopaenia,

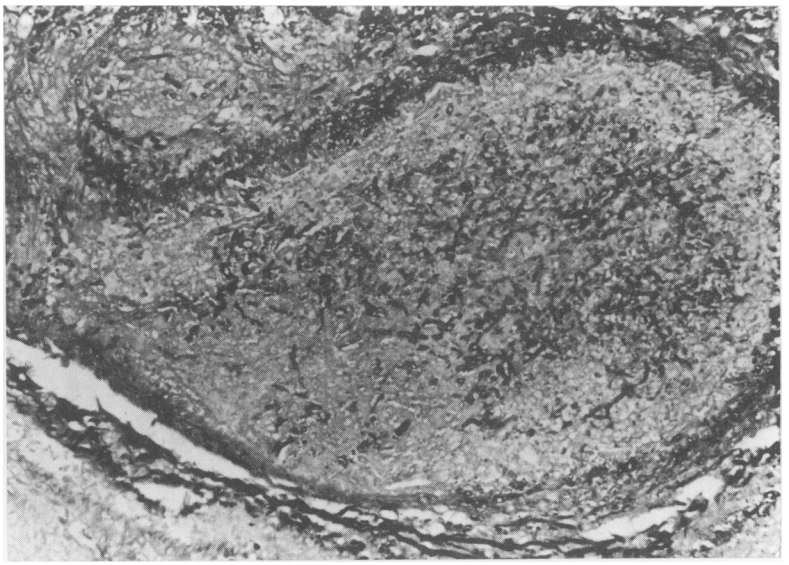

FIG. 2. Large pulmonary artery which contains thrombus composed of packed fibrin and dichotomous hyphae consistent with *Aspergillus*. At the upper edge of the vessel, hyphae are seen to completely penetrate the vessel wall, extending into the adjacent infarct (×66—Grocott stain).

which these patients often suffer, seems to confer some protection, patients with very low platelet counts are nevertheless at risk (Wiernick and Serpick, 1969; Needleman, Stein and Hoak, 1981). Thus, a high index of suspicion for pulmonary embolus must be maintained by the clinician in the care of the cancer patient.

In recent years, many of the cellular and molecular phenomena which initiate and regulate inflammation or thrombosis have been shown to be interrelated. A number of mediators of platelet adhesion and aggregation (e.g. ADP, epinephrine) potentiate leucocyte adhesion; conversely, non-steroidal anti-inflammatory agents inhibit platelet aggregation as well as leukocyte adhesion. The platelet can be a source of lysozomal enzymes which are important in inflammation, as well as leucocyte chemotactic factors such as hydroxyeicosatetraenoic acid (HETE); moreover, in certain situations, the leucocyte releases procoagulant material, a process which is, in turn, enhanced by platelet divided lipids (Needleman and Hoak, 1982). Study of the plasma proteins as well, have yielded potential interfaces of thrombosis and inflammation, such as activation of complement, Hageman factor, Fletcher factor and others (Ratnoff, 1980). The precise relationship of these patients' thromboemboli to their development of diffuse interstitial pneumonitis remains unclear. However, it is tempting to speculate that the microthrombi in the small interstitial vessels might be related to interstitial inflammation through activation of both processes at one or more of these interfaces.

The possibility that these were 2 independent processes involving different regions of the lungs must be addressed, in view of lung biopsies in each patient which failed to establish the diagnosis of thromboembolism. The diffuse nature of the pneumonitis on X-ray as well as the extensive diffuse fibrosis at autopsy mitigate against topographic separation of the processes. Rather, it seems that in the lung periphery where biopsies are performed, the thromboemboli involve microscopic vascular structures, and are themselves miniscule. The minute emboli are probably the most readily resolved by fibrinolytic enzymes. Thus, it seems that open lung biopsy in these patients might examine a portion of lung where resolution of the thromboembolism precedes that of interstitial inflammation.

It is also conceivable that the cytolytic chemotherapy, which both patients received, contributed to the development of diffuse interstitial pneumonitis. While none of the drugs given have been firmly associated with interstitial pneumonitis, one cannot exclude the possibility that any of the drugs, alone or in combination could give rise to inflammation as a result of direct toxicity to vascular endothelium or idiosyncratic hypersensitivity. In addition, neutropenia induced by these drugs could predispose to thrombosis by removing the fibrinolytic and/or anticoagulant activities of granulocytes from the blood (Needleman *et al.*, 1981).

A significant number of thrombopenic patients who suffer thromboembolism will have occult fungal infection as did Case 2 (Needleman *et al.*, 1981).

Many fungi are heavily endowed with proteolytic capacities which can directly cause both inflammation and thrombosis. Alternatively, the ability of these organisms to invade vessel walls and adjacent tissue (Fig. 2), can cause lysozomal enzymes and tissue thromboplastin to be released from the tissue, initiating both processes (Needleman *et al.*, 1981).

The treatment of neoplastic disease depends heavily on the quality and diligence or supportive care in preventing and recognizing non-malignant complications. The importance of pulmonary embolism in this regard can not be overemphasized. The clinician's index of suspicion should not be too greatly diminished by the presence of thrombocytopenia, even if severe (Wiernick and Serpick, 1969; Needleman *et al.*, 1981). Diagnosis can be difficult, owing to the numerous, non-specific manifestations of the disease. These cases suggest that a lung biopsy diagnostic of diffuse interstitial pneumonitis should be added to the wide variety of findings which can be observed in patients with pulmonary embolism.

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(*Accepted* 25 *November* 1982)