Aspergillus-related aortic thrombosis

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The increasing number of immunocompromised patients seen in general and hospital practice means that opportunistic infections such as disseminated aspergillosis are being encountered more and more often. The clinical diagnosis is difficult in early disease because of the nonspecific manifestations. It may also be missed in more advanced disease, as there is a tendency to attribute symptoms and signs to concomitant bacterial infections, which are often present.[1]

We report a case of disseminated aspergillosis with a unique complication, spontaneous thoracic aortic thrombosis, that was masked by concurrent bacterial sepsis.

Case report

Acute lymphoblastic leukemia was diagnosed in a 6-year-old girl in May 1983 after she had presented with fever, sore throat and malaise. Initially she responded well to induction and maintenance chemotherapy with intrathecally administered methotrexate and to central nervous system irradiation. She remained asymptomatic for 18 months, before suffering her first relapse, in October 1984. At that time her bone marrow cells were all blast forms, and she was treated with vincristine sulfate, cyclophosphamide, doxorubicin hydrochloride and prednisone, with good response. Over the next few months she was treated with acyclovir for herpes zoster of her left shoulder and arm and underwent appendectomy for acute appendicitis. A second relapse, in December, responded only partially to courses of chemotherapy with vincristine, doxorubicin, cytarabine, prednisone, cyclophosphamide and mitoxantrone. She underwent permanent central-line insertion for continued chemotherapy in February 1985.

Serious chemotherapy-related problems began to appear, and the patient presented on two occasions with gum bleeding, epistaxis and melena due to chemotherapy-induced thrombocytopenia (platelet count 5×10^9/L). She also had intermittent fever, which was attributed to α-hemolytic streptococcal septicemia and treated with a course of cephalexin and cotrimoxazole, with initial clinical improvement. She received several blood and platelet transfusions for anemia (hemoglobin level 7.8 to 10.9 g/L) and thrombocytopenia (platelet count 5 to 330×10^9/L.

In June 1985 the patient was again admitted with melena and fever, and blood cultures again revealed α-hemolytic *Streptococcus*. She was treated with broad-spectrum antibiotics (cefamandole nafate, tobramycin, cotrimoxazole and penicillin) and a new chemotherapy regimen (L-asparaginase and methotrexate) because of continuing high blast counts and clinical deterioration. Within the month she presented moribund, with fever, nonspecific malaise and pain in her left flank. There had been no cough, dyspnea or bleeding. Physical examination revealed left basal rhonchi and hepatosplenomegaly. The patient died several hours after admission. The clinical diagnosis was acute lymphoblastic leukemia and streptococcal sepsis.

Autopsy revealed focal mild to moderate lymphoblastic infiltrates in the liver, lymph nodes, spleen and ovaries, hepatosplenomegaly and paraaortic lymphadenopathy. Complications of systemic and intrathecal chemotherapy and of repeated blood transfusions included marked alopecia, bone marrow hypoplasia, cutaneous petechiae, mild dilatation of the cerebral ventricles, sepsis due to α-hemolytic *Streptococcus* and moderate hemosiderosis in the liver, spleen and bone marrow.

Two target lesions of early aspergillosis were found in the left lung (Fig. 1), associated with numerous mycotic thromboemboli in the thoracic segment of the descending aorta, left lung, liver, spleen, kidneys, periadrenal vessels and meninges. Fungating through the os of a mediastinal branch of the thoracic aorta was a 5-cm-long thrombus that had totally occluded the aortic lumen (Fig. 2). The walls of the aorta and its thoracic branches were not, however, infiltrated by *Aspergillus* hyphae. There were numerous mycotic thromboemboli in the lungs that had produced large hemorrhagic infarcts in the left lower lobe, but there was no mediastinal infiltration by the fungus. The splenic artery showed plugging by fungal hyphae associated with extensive infarction of the spleen. Thromboemboli were present in smaller vessels of the kidneys and liver, with numerous infarcts. There were thromboemboli in several periadrenal vessels, with moderate left adrenal and slight

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periadrenal hemorrhage. Bacterial clusters were seen within vascular lumina of many visceral organs as well as within pulmonary alveoli; however, since the patient had been neutropenic, there was no acute inflammatory cell reaction to the clusters.

The cause of death was septicemia due to α-hemolytic *Streptococcus* and disseminated aspergillosis complicating secondary immunosuppression in a leukemic patient.

Postmortem culture of venous blood and of tissue from the edge of an infarcted area of lung yielded no evidence of *Aspergillus*, although α-hemolytic *Streptococcus* was identified.

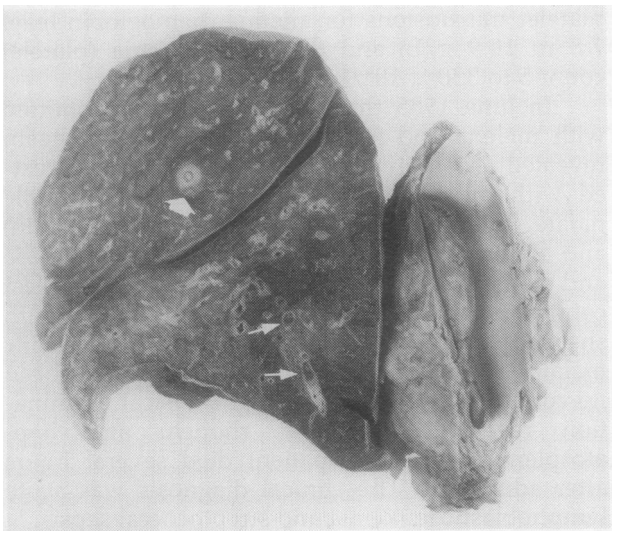

Fig. 1 — Sagittal section of left lung, with adjacent thrombosed aorta opened to reveal thrombus extending distally from just below ligamentum arteriosum. Single target lesion is present in upper lobe, with adjacent thrombosed vessel (large arrow) and central area of necrosis. Lower lobe has infarct, with numerous thrombosed vessels (smallow arrows) and second target lesion (not shown).

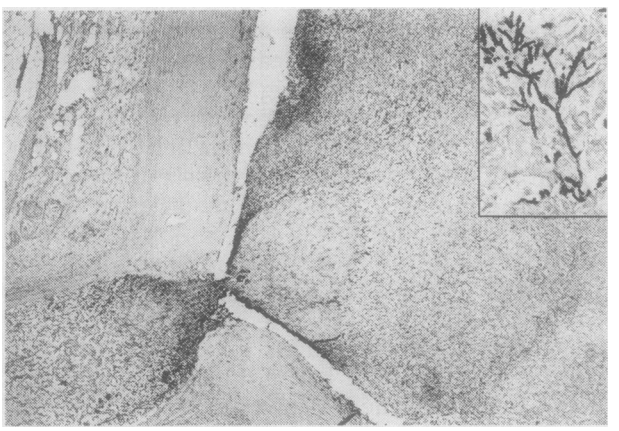

Fig. 2 — Mediastinal branch of aorta, occluded by mycotic thromboembolus (hematoxylin-eosin and methenamine-silver nitrate; original magnification × 8, reduced approximately 50%). Inset: typical septate *Aspergillus* hyphae within thrombus (methenamine-silver nitrate; original magnification × 125, reduced approximately 50%).

Comments

This case shows that invasive aspergillosis can cause spontaneous thrombosis of vessels of any size, including the thoracic aorta. The aortic thrombosis was not, however, caused by contiguous spread from the adjacent infected lung, as serial sectioning of the entire thrombosed segment of the thoracic aorta and adjacent para-aortic tissues failed to reveal any direct transmural spread of fungal hyphae to the occluded aorta or mediastinal branches. Only minor intimal infiltrates were seen adjacent to the thrombus. Rather, aortic thrombosis was due to the more usual smaller-vessel thromboembolism into a mediastinal branch of the aorta. This phenomenon has previously been well documented.[2] Embolization in our case occurred from the primary pulmonary site, where the early target lesions of invasive aspergillosis could still be seen.[3] These target lesions and the thromboemboli were heavily infiltrated with the characteristic septate, dichotomously branched, narrow (3 to 5 μm) *Aspergillus* hyphae[4] (Fig. 2). The serious complication of aortic thrombosis had resulted from backgrowth of fungal hyphae into the aortic lumen. That such a major complication was not clinically suspected is hardly surprising, given its rarity and the moribund status of the patient.

The failure to grow *Aspergillus* on venous blood culture is also not surprising, as the results are usually negative in subsequently proven cases.[3] This may be due to filtering of the long fungal hyphae by the capillary bed or to the intermittent nature of fungal embolization.[5] If so, culturing many samples of arterial rather than venous blood may be one way to achieve a higher yield of positive results. The negative results of tissue culture resulted from sampling infarcted rather than viable infected lung tissue.

This case illustrates yet another previously undescribed, serious manifestation of disseminated aspergillosis. Invasive pulmonary aspergillosis should be considered in febrile, immunocompromised patients, particularly if chest radiography shows an infiltrate that fails to respond to antibiotics.[3]

References

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