

Pulmonary aspergillus infection invading the pleura

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ABSTRACT During a 10-year-period, six patients with non-postoperative aspergillus infection of the pleura were seen. In all patients a pulmonary aspergillus infection had been present for some years. The fungus invaded the pleura, causing a bronchopleural fistula and a cavity in the pleural space. A prerequisite for the pleural aspergillosis was that the lung and pleura were previously damaged, usually by therapeutic pneumothorax for active tuberculosis some decades earlier. The fungus can cause destruction of the lung and death of the patient from the chronic infection unless treated. The best treatment is early excision of the pleura with resection of the upper lobe or if necessary the whole lung. To reduce the risk of postoperative aspergillus empyema, the patient should be treated with antifungal agents before and after operation. In inoperable patients, local antifungal treatment may clear the infection but is not always effective.

Aspergillus infection of a previously damaged lung is not uncommon. This fungus is usually regarded as saprophytic, of importance mainly because of occasional allergic reactions or haemoptyses. Only in immunocompromised patients has it been considered to be invasive. Pleural infection by aspergillus is regarded as a superinfection of a preformed cavity in the pleura or a post-operative complication. However, the fungus can be invasive in a fibrotic pleura in a non-immunocompromised host, as seen from the following cases.

Patients

From 1969 to 1979, six patients with non-postoperative pleural aspergillosis have been diagnosed. Five of them were treated with pneumothorax for active tuberculosis some decades earlier, leaving a fibrosed pleura, in some cases with calcification but without any cavities or remarkable thickening (table 1). At least two patients (cases 2 and 6) had had symptoms that could be attributable to an aspergillus infection of the lung for some years before the present disease manifestations. Two had received anti-tuberculous chemotherapy despite the fact that no bacilli or signs of active tuberculosis could be found (cases 1 and 2).

All patients presented with signs and symptoms of chronic infection of some months duration—namely, loss of weight, malaise, cough, raised sedimentation rate, and anaemia.

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The diagnosis of aspergillosis was established by serological tests, and by fungal growth from the pleura and in some cases also the sputum (table 2). All patients had high titres of precipitins against *Aspergillus fumigatus* in their blood. Biopsies of pleura showed non-specific fibrosis and granulomas, and only when specimens from an actual mycetoma were examined could the diagnosis be made from pathological findings.

Aspergillus fumigatus was grown from the pleural fluid in all cases, but repeated samples were often necessary. In one empyema anaerobic streptococci were found twice, but otherwise no other suspect pathogens were grown. Anaerobic cultures were not performed in all cases, however, and coexistence of such bacteria is therefore possible. With the appearance of the first symptoms, all patients were treated by their general practitioners with penicillin and broad spectrum antibiotics, generally in repeated courses, without improvement, which indicates that if bacteria were present their importance was only minor.

Four patients underwent operation. Two of them recovered uneventfully. Both underwent lobectomy and decortication only, and one of them had preoperative treatment with antifungal drugs. In the other two, extension into the lung of the pleural fibrotic tissue and parenchymal destruction necessitated pneumonectomy. Both of these patients developed a postoperative empyema from which *A. fumigatus* was grown. Neither had had preoperative antifungal treatment. After intensive local treatment the empyema in one of the patients cleared and he is

Table 1 *Clinical data*

Case	Year of birth	Sex	Therapeutic pneumothorax	Symptoms from Jungal infection	X-ray (numbers refer to figures)	Anti-tuberculous treatment	Steroid treatment	Anti-fungal drugs	Operation	Course
1	1926	M	Bilateral 1946-57	Jan 1972: productive cough weight loss malaise	May to Sept 1972: progressive changes left side (1a-h)	May 1972 to Aug 1973	None	None	Upper lobectomy + decortication	Uneventful. Alive, respiratory invalid
2	1916	F	Bilateral 1936-47	Since 1965 cough, haemoptyses, asthma. 1971: weight loss, fever	1947 to 1963 apical scars 1963: progression. 1971: pyopneumothorax (2 a-d)	1963-65	1965-67	Local amphotericin B	Inoperable	Died 5 months after first sign of pleura in pleura
3	1896	M	Left 1944	1969 cough, fever, loss of weight	1969: aspergilloma left. 1970: pyopneumothorax	1960-61 (positive sputa)	None	None	Operation declined	Died after few months
4	1921	M	Right, 1950-55	1969: malaise, fever, cough, loss of weight	1955-60 apical scars. 1960 to 1969: slow progression. 1969: pyopneumothorax (3 c-e)	None	None	Local + systemic after operation	Decortication + pneumonectomy	Postoperative empyema after 4 months' hospital treatment now in good health
5	1921	M	None	Cough for many years. May 1979: worse, dyspnoea, fever, loss of weight	1978: Apical scarring. May 1979: progression. Postop infiltrates other side (4 a-b)	None	None	Local + systemic after operation	Decortication + pneumonectomy	Postoperative empyema died of aspergillus pneumonia 5 months after operation (verified at necropsy)
6	1918	F	Right, 1943-44	1973-78 cough. Dec 1978: loss of weight, subfebrile	Until 1973, apical scarring. May 1979: aspergilloma and pleural cavity (5)	None	None	Systemic 2 weeks before and 2 weeks after operation	Decortication + lobectomy	Uneventful remains in good health

Table 2 *Diagnosis of aspergillosis*

Case	IgE	Precipitin titre	Fungal sputum	Growth from pleura	Pathological findings
1	Negative	High	Positive	Not done	Fibrosis with granulomas
2	Not done	High	Positive	Positive	Abscesses, granulomas
3	Not done	High	Negative	Not done	No necropsy
4	Negative	High	Negative	Positive	Chronic fibrosis, granulomas
5	Negative	High	Negative	Positive	Necrotic areas, granulomas, hyphae in aspergilloma
6	Negative	High	Positive	Positive	Typical hyphae in aspergilloma, otherwise fibrosis

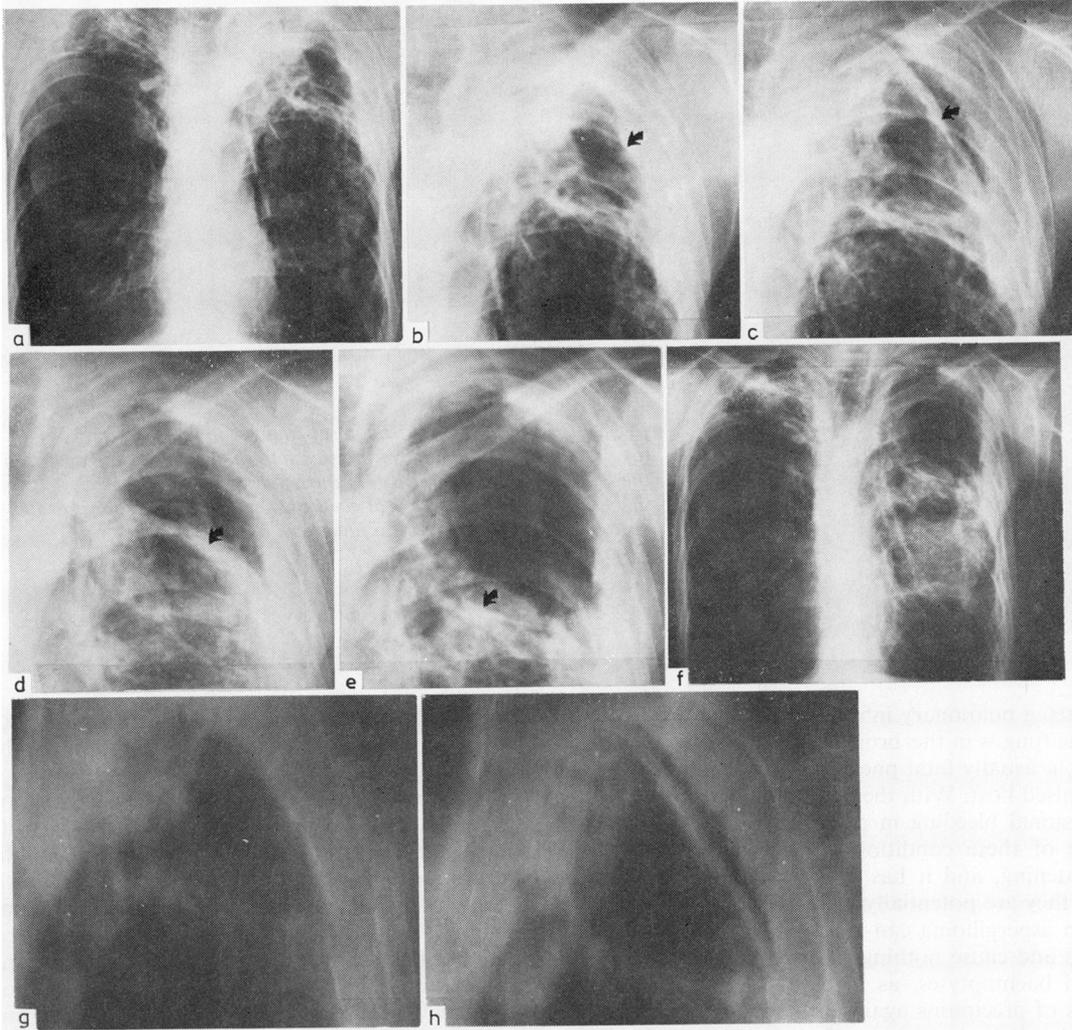


Fig 1 *Case 1. (a) May 1972: apical scarring bilaterally. (b-e) development of pleural apical cavity on left side. (b) May 1972, close-up of a; (c) July; (d) September; (e) October, close-up of f; (f) The arrow points to the same small calcification within the visceral pleura. (g) tomogram May; no air in the pleura. (h) Tomogram July; air separating the visceral from the thickened parietal pleura.*

now well, but in the other the empyema persisted and the patient died of aspergillus pneumonia in the remaining lung despite systemic and local antifungal treatment.

Two patients were not operated on. Both succumbed to their infection, one of them despite local antifungal treatment.

Discussion

Aspergillus infection of the lung is not uncommon among patients attending a chest department.^{1,2} Three clinical types are usually described: aspergilloma—that is, a fungus ball within a cavity; allergic bronchopulmonary aspergillosis, with eosinophilia,

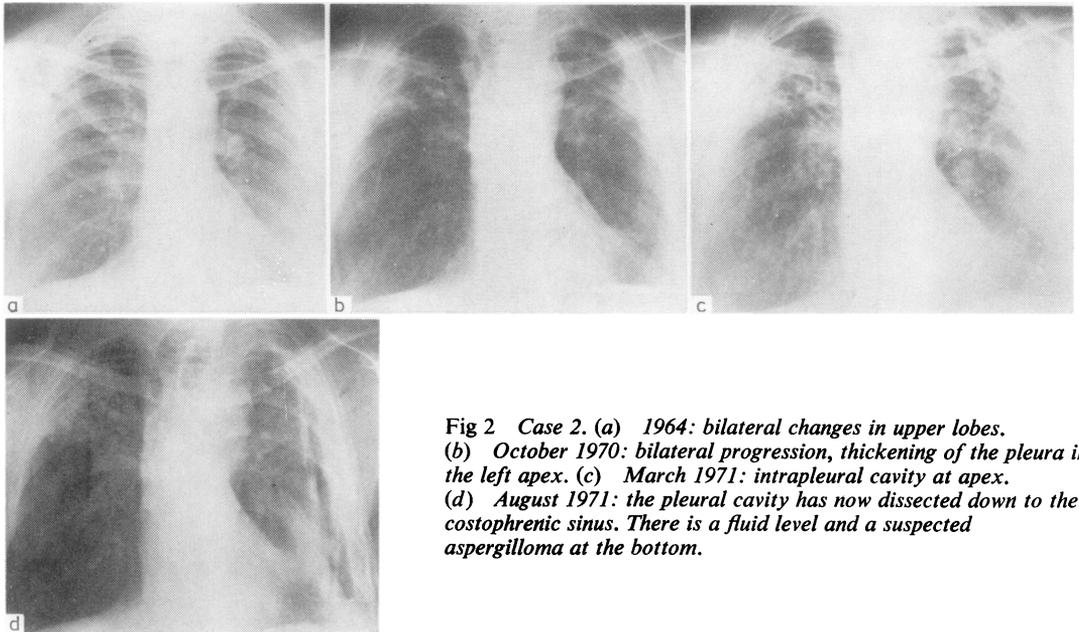


Fig 2 Case 2. (a) 1964: bilateral changes in upper lobes. (b) October 1970: bilateral progression, thickening of the pleura in the left apex. (c) March 1971: intrapleural cavity at apex. (d) August 1971: the pleural cavity has now dissected down to the costophrenic sinus. There is a fluid level and a suspected aspergilloma at the bottom.

recurring pulmonary infiltrates, asthma, and growth of the fungus in the bronchi; and invasive aspergillosis, a usually fatal pneumonia in an immunocompromised host. With the exception of the latter, and occasional bleeding in patients with aspergillomas, none of these conditions is considered to be life threatening, and it has only recently been realised that they are potentially progressive.³

An aspergilloma can reside in the lung for many years and cause nothing more than slight cough or small haemoptyses, as in cases 2, 5, and 6. High titres of precipitins against the fungus are found in the blood. As seen in cases 2, 4, and 6, the fungus can be locally destructive in a previously damaged lung and form a cavity. This usually takes place at the apices, and the radiographic changes will often be interpreted as reactivation of tuberculosis.¹ Cases 1 and 2 are good examples of this. It has been stated that antituberculous drugs increase the risk of aspergillus infection. This idea may possibly result from a diagnosis of the real cause of the changes some time after the wrong treatment (that is, anti-tuberculous drugs) has been given.

A typical sign of aspergillus growth in a lung cavity is thickening of the pleura overlying it.^{4,5} It is unclear whether this is caused by actual fungal growth or by an immunological reaction.⁴ Since the precipitins remain high, a constant challenge by the fungus must take place—most probably by growth in the “capsule”. In the cases described here the

spread of the pleural thickening down to the costophrenic angle before cavitation strongly supports the growth theory.

There is an intense reaction to the fungus, making it virtually impossible for the pathologist to identify it in the thick fibrotic tissue. If the defences of the host are not adequate for some reason, the fibrotic tissue will spread and then break down, emptying through a bronchopleural fistula. Once a pleural cavity has formed, it will grow, causing collapse and destruction of the lung. An aspergilloma can develop in the cavity. The parietal pleura becomes thick and nodular, “pseudomesotheliomatous”,⁶⁻⁸ as seen in figs 1, 2 c-d, 3 c-e.

Unless the development is closely followed radiologically, it is difficult to judge in the final stage, either at operation or autopsy, whether the cavity is parenchymal or pleural. For example, in 1977 a case report showed a mycetoma migrating from the top to the bottom of the lung, presumably as a result of lung destruction by coexistent tuberculosis.⁹ This was more likely invasive pleural aspergillosis. It is not merely an academic question, since the treatment is different if the fungus is regarded as the main pathogen.

Fever, malaise, and a high sedimentation rate in mycetoma patients were described in 1970.¹⁰ In the published illustrations considerable pleural thickening can be seen, and cure was by pneumonectomy. Thus, the findings can be explained by fungal in-

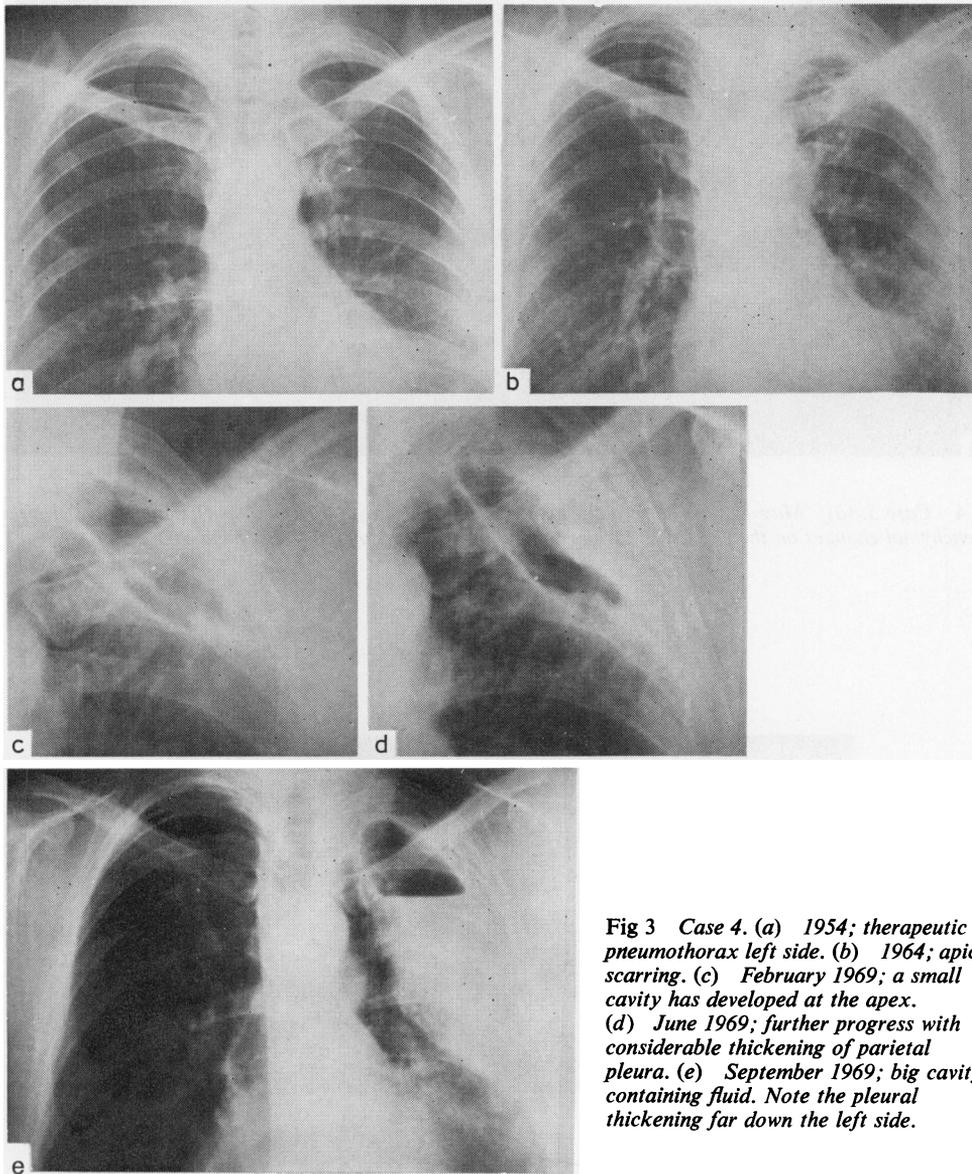


Fig 3 Case 4. (a) 1954; therapeutic pneumothorax left side. (b) 1964; apical scarring. (c) February 1969; a small cavity has developed at the apex. (d) June 1969; further progress with considerable thickening of parietal pleura. (e) September 1969; big cavity containing fluid. Note the pleural thickening far down the left side.

vasion rather than the antigen-antibody reaction suggested by the authors.^{10 11}

There are a number of reports of cases with pleural aspergillosis, many of which might well be caused by fungal pleural invasion rather than superinfection of an empyema caused by some other agent.^{6 7 12-20}

Invasive pleural aspergillosis is potentially fatal, and the treatment of choice seems to be decortica-

tion. This should be done early to avoid progressive deterioration of the patient's general condition and destruction of the lung, which would then necessitate pneumonectomy. Early operation will probably also reduce the risk of postoperative aspergillus empyema. To reduce this risk further, preoperative systemic (and if possible local) treatment with antifungal agents should be given.

In inoperable patients, local treatment with anti-

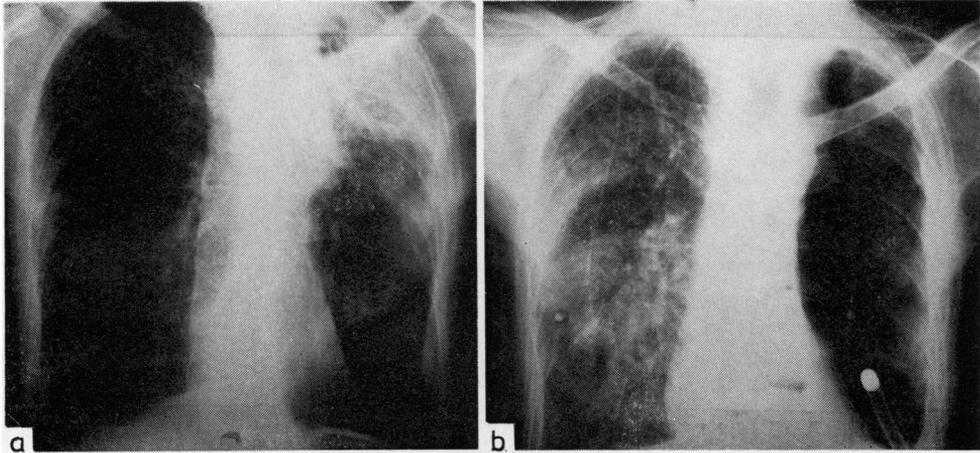


Fig 4 Case 5. (a) May 1979; widespread changes at left apex. (b) After left pneumonectomy: progressive parenchymal changes on the right side. At necropsy *aspergillus pneumonia* was found.

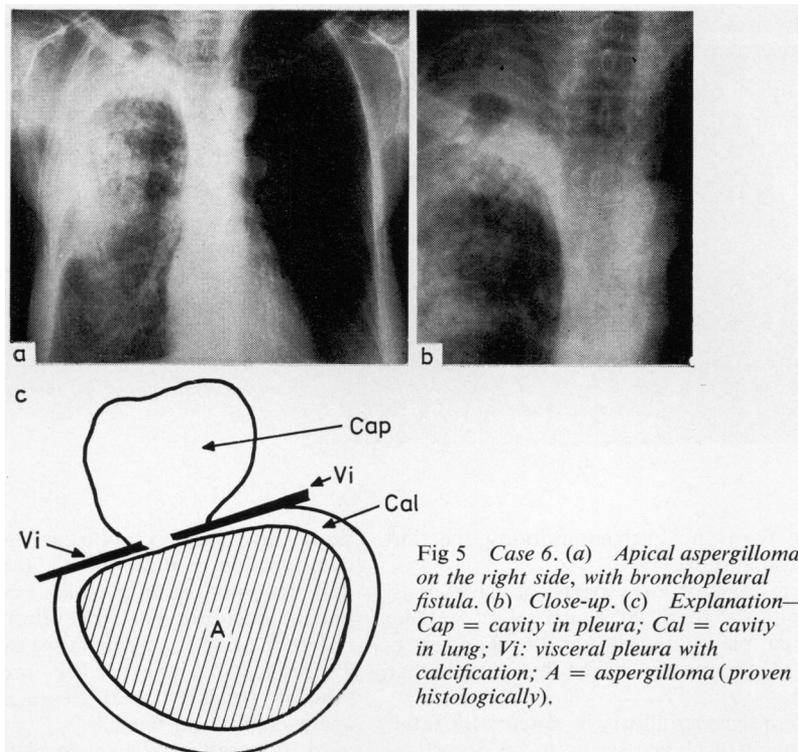


Fig 5 Case 6. (a) Apical aspergilloma on the right side, with bronchopleural fistula. (b) Close-up. (c) Explanation—Cap = cavity in pleura; Cal = cavity in lung; Vi: visceral pleura with calcification; A = aspergilloma (proven histologically).

fungal drugs has been reported to give good results in aspergillus empyema,^{6 7} but as seen from cases 2 and 5, this will not always lead to cure. This is understandable in view of the thick fibrous tissue in which the fungus grows—penetration of drugs therein must be very slow.

Aspergillus pneumonia, as occurred in case 5, is very rare in patients without a malignant condition or not having immunosuppressive treatment. The poor general condition of the patient because of the long-standing empyema was probably a predisposing factor. Antifungal treatment was of no avail.

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