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Papers

10 year review of invasive aspergillosis detected at necropsy

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Abstract

Between 1980 and 1989, 32 cases of invasive aspergillosis were identified out of 2315 consecutive necropsies, an incidence of 1·4%. The incidence in immunosuppressed "high risk" patients was 10·7%. Twenty out of 32 cases showed spread beyond the lungs, with the brain the most common site. There was an increase in cases in the second half of the decade, attributable to the start of a liver transplantation programme. Liver transplant recipients and patients with haematological malignancies were at significantly greater risk of acquiring aspergillosis than kidney transplant recipients or those with solid malignancies treated with chemotherapy. There was also a greater risk of haematogenous dissemination in liver transplant recipients than in all other groups, and this was significantly associated with the use of high dose steroids as anti-rejection treatment. *Aspergillus* was isolated during life in only eight cases, which indicates a continuing need for and emphasises the value of necropsy.

Invasive aspergillosis is a serious complication of immunosuppressive treatment or diseases which profoundly impair normal immunity. The increasing use of cytotoxic drugs in the treatment of malignant disease and the rising number of organ transplants is expected to result in a substantial increase in the number of cases. Few cases are recognised in life, however,[1] and the disease is more likely to be first diagnosed at necropsy. We therefore reviewed all necropsy records covering the years 1980–89 at one centre to identify the categories of patient most at risk, any important aetiological factors, changes in the incidence of the disease and the value of the necropsy in establishing the diagnosis.

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Methods

The records of all 2315 necropsies carried out between 1980 and 1989 by the pathology department of the Queen Elizabeth Hospital, Birmingham, were reviewed. Two hundred and ninety nine patients conventionally regarded as at increased risk for aspergillosis were identified ("high risk" group). Criteria for inclusion in this group were the following: solid organ transplantation (n = 71 liver and 41 kidney); haematological malignancy (n = 154), treated or untreated (including aplastic anaemia, lymphoma, and 16 bone marrow transplant cases); patients treated for solid malignancies with cytotoxic chemotherapy within three months of death (n = 33).

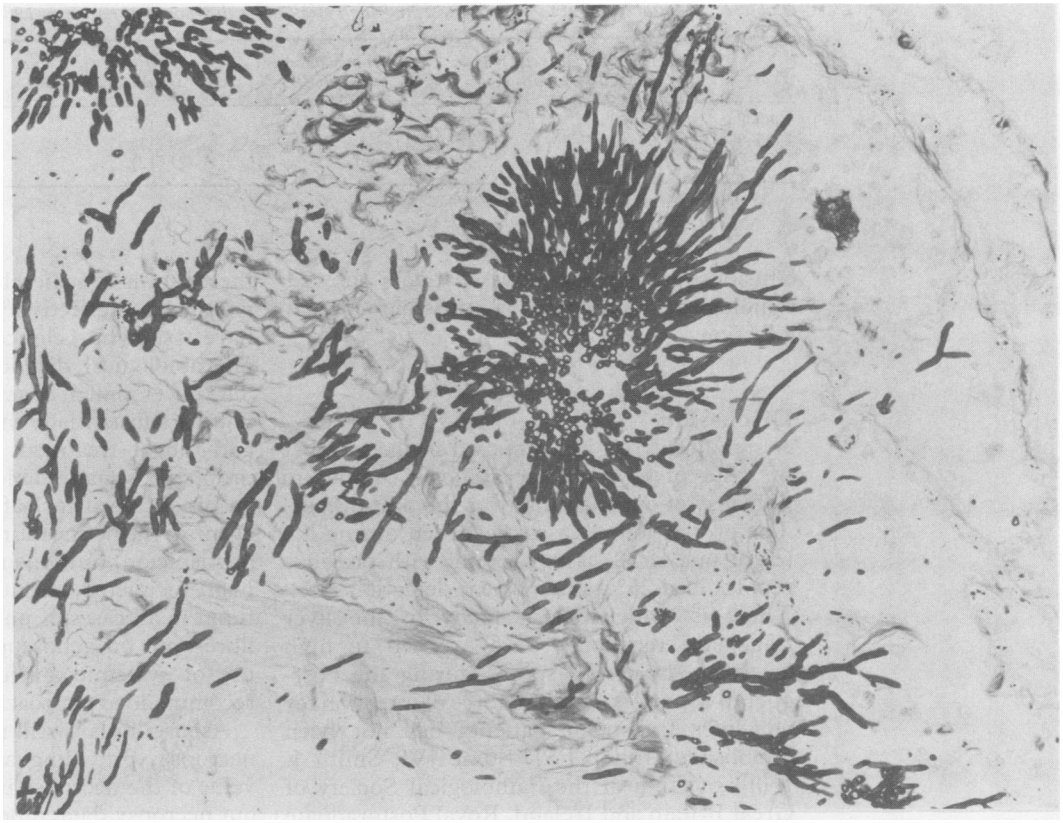
Where *Aspergillus* infection was mentioned in the macroscopic description or histology report, slides were reviewed to confirm the diagnosis and determine the extent of tissue disease. Visualisation of regular, dichotomously branching, septate hyphae with unequivocal evidence of tissue infiltration was necessary for classification as invasive aspergillosis (figure). The clinical records of each case were examined and particular note made of chest *x* ray reports, neutrophil counts, liver function, steroid and anti-fungal treatments during the final weeks of life. Any antemortem isolation of *Aspergillus* was recorded.

Statistical analysis was carried out using fourfold tables of the χ^2 test, with Yates's correction where appropriate. Probabilities were calculated with one degree of freedom.

Results

Forty cases of *Aspergillus* infection were identified. Thirty two (1·4% of all necropsies and 10·7% of "high risk" cases) showed invasive disease on histological examination; the remainder were aspergillomas or instances of non-invasive bronchial colonisation and were not considered further. Patients with invasive disease included 16 who had haematological malignancies (including four bone marrow transplant cases), 12 with liver transplants, and one with a kidney transplant. Three patients did not fall into the "high risk" group: one developed major systemic complications following vascular surgery, one had α1 antitrypsin deficiency and emphysema, and one was treated for polyarteritis using high dose steroids. There were 15 males and 17 females with a mean age of 45·0 years (range six months to 76 years).

The pattern of incidence year by year is shown in table 1. Between 1980 and 1984, 10 cases of aspergillosis were identified out of 1219 necropsies (0·8%), nine of which occurred in 146 potentially "high risk" patients (6·2%). In 1985–89 there were 22 cases—2·0% of 1096 necropsies. Twenty of these occurred in 153 "high risk" cases (13·1%). The difference is significant whether related to all necropsies or as a proportion of "high risk" patients ($p < 0·05$ and $p < 0·02$, respectively). Although the total number of necropsies decreased over the decade, there was no significant



Branching septate hyphae crossing pulmonary tissue boundaries: essential for confirmation of invasive aspergillosis.

increase in the proportion of "high risk" cases, implying a change in the relative risk within this group. Although environmental factors may be important, study of the different patient categories showed changes in the composition of the "high risk" group (table 2). There was a clear decrease in the number of cases of solid malignancies treated with cytotoxic drugs, more modest falls in kidney transplant and haematological cases, but no change in bone marrow transplant cases. The sharp increase in liver transplant recipients was attributable to the start of a major liver transplantation programme in the middle of the decade.

Histological evidence of primary pulmonary infection was found in all but a kidney transplantation case: inadequate sampling was probably responsible as the gross appearances were consistent with *Aspergillus* pneumonia (table 3). Spread beyond the lungs was present in 20 cases. These included 11 of the 12 liver transplant cases but only six of the 16 haematological cases, or nine of the 20 non-liver transplant cases. These differences are significant ($p < 0.02$ in both instances). The brain was the commonest site of extrapulmonary disease in the entire series, but was affected significantly more frequently in liver transplant recipients (10 out of 12 cases) than in haematological patients (three out of 16; $p < 0.01$) and non-liver transplant cases (six out of 20; $p < 0.02$). A comparison of the total number of sites affected in the liver transplant cases with those in haematological and non-liver transplantation groups showed even greater significant differences ($p < 0.001$ in both cases).

Because we have previously shown a highly significant association between the incidence of cerebral aspergillosis and total cumulative steroid dosage in liver transplantation,[2] we considered this factor worthy of further analysis. Twelve out of 20 patients with evidence of haematological spread—that is, disease in other than lung or gastrointestinal tract—received high dose steroids compared with three out of 14 with pulmonary, oesophageal, stomach or bowel disease ($p < 0.05$). The incidence of cerebral disease in the treated group (12 out of 15 patients) differed even more significantly from that in the untreated group (four out of 17; $p < 0.01$). Differences between the two groups in numbers of histologically confirmed, affected sites beyond the lungs and the gastrointestinal tract were highly significant ($p < 0.001$). There was, however, no correlation between a low neutrophil count (less than $0.1 \times 10^9/l$) and systemic disease.

In 19 cases no microbiological isolation of *Aspergillus* was made before necropsy, and in a further five cases, positive results were only obtained after death. In the 30 cases where chest *x* ray reports were available, an unqualified diagnosis of pneumonia was made in 23 cases and non-specific changes (oedema or

Table 1 Annual incidence of aspergillosis diagnosed at necropsy 1980–89

Year	No of necropsies	No of "high risk" cases (% necropsies)	No of aspergillosis cases (% necropsies; % "high risk" cases)
1980	256	34 (13·3)	1 (0·04; 2·9)
1981	213	21 (9·9)	3 (1·41; 14·3)
1982	263	30 (11·4)	3 (1·14; 10·0)
1983	268	29 (10·8)	2 (0·07; 6·9)
1984	219	32 (14·6)	1 (0·05; 3·1)
1985	264	26 (9·8)	6 (2·27; 23·1)
1986	239	28 (11·7)	2 (0·08; 7·1)
1987	228	38 (16·7)	8 (3·51; 21·1)
1988	188	31 (16·5)	3 (1·60; 9·7)
1989	177	30 (16·9)	3 (1·69; 10·0)
1980–89	2315	299 (12·9)	32 (1·38; 10·7)

Table 2 Annual incidence of aspergillosis in "high risk" cases diagnosed at necropsy 1980–89

Year	Haematological cases Total (aspergillosis)	Kidney transplant cases Total (aspergillosis)	Liver transplant cases Total (aspergillosis)	Solid malignancy cases Total (aspergillosis)
1980–84	91 (8)	24 (0)	7 (1)	24 (0)
1985–89	63 (8)	17 (1)	64 (11)	9 (0)
1980–89	154 (16)	41 (1)	71 (12)	33 (0)

effusions) in five; only two patients showed radiological evidence of possible fungal infection.

Discussion

A significant rise has occurred in the number of cases of invasive aspergillosis coming to necropsy at our institute over the past decade. The proportion of cases diagnosed during life (eight out of 32) is in keeping with previous reports of a 25% antemortem detection rate.[1] There is evidence that many of the liver transplant recipients were exposed to high levels of *Aspergillus* spores during the post-operative period, but the source of infection for non-liver transplant patients has not been established (Elliot TSJ, Stone JW, Smith J. 160th meeting of the Pathological Society of Great Britain and Ireland, Royal Postgraduate Medical School, 1990).

It is noteworthy that three patients did not fall into our "high risk" group, although one had received steroids in high doses. The occurrence of aspergillosis outside conventionally defined immunocompromised groups is generally underrecognised, but has been the experience of other authors.[3–5]

Several factors might account for the high incidence of disseminated aspergillosis in liver transplant recipients relative to other groups. These include liver failure,[3] inappropriate anti-rejection treatment, operative difficulties, and prolonged artificial ventilation.[2] Although data in our present study were insufficient to determine any differences in total cumulative steroid dose, or explore the role of liver failure, high dose steroids seem to be a most important factor in haematogenous dissemination. There was no obvious explanation for the particularly strong correlation with cerebral disease. Although absolute neutropenia showed no association with the risk of developing widespread disease, clearly many patients were *relatively* neutropenic in the context of overwhelming systemic infection.

The importance of diagnosing *Aspergillus* pneumonia before extrapulmonary spread occurs has been emphasised.[5] Prognosis thereafter is considerably worse and treatment is usually ineffective.[6] Unfortunately, as we have shown, clinical, radiological, and microbiological diagnoses remain unreliable. The development of serological techniques has not yet substantially improved this.[7 8] Current anti-fungal treatment is toxic and systemic prophylaxis inadvisable: it is clear that there is an urgent need for safer systemic anti-fungal agents.[9] In the meantime a high clinical index of suspicion, cautious use of steroids in transplant recipients, strenuous attempts to isolate fungi in all cases of pneumonia, preferably by fibre-optic bronchoscopy[10] and early aggressive use of systemic antifungal treatment is our recommended approach.

Aspergillosis is still most often diagnosed at necropsy, providing another example of the value of the necropsy in clinical audit.[11] Without necropsy data, much of this disease would remain undetected, giving rise to a serious underestimate of its incidence and importance.

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Table 3 Histological evidence of invasive aspergillosis

	Lung	Brain	Heart	Kidney	Thyroid	Bowel	Oesophagus	Liver	Pancreas	Spleen	Stomach	Skin
Haematological cases (n = 16)	16	3	3	3	3	3	3	1	2	1	1	1
Liver transplant cases (n = 12)	12	10	7	6	4	3	3	4	2	2	3	1
Kidney transplant case (n = 1)	0*	1	0	0	0	0	0	0	0	0	0	0
Other cases (n = 3)	3	2	2	2	1	1	0	0	0	1	0	0
Total (n = 32)	31	16	12	11	8	7	6	5	4	4	4	2

*Grossly, this was typical pulmonary aspergillosis.