Candida infection of the oesophagus

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Candida infection of the oesophagus is not common but because the symptoms are so unpleasant and potentially curable it should be recognized quickly.

This paper concerns the 13 adult patients with oesophageal candidiasis seen in Oxford during the last 10 years. Many had been receiving neither antibiotics nor corticosteroids and thereby differ from the majority of cases described previously. Some of the patients had serious blood disease associated with severe neutropenia.

DESCRIPTION OF PATIENTS

The clinical data concerning the patients are summarized in the Table. There were 10 females and three males and their ages ranged between 33 and 89 years. Three patients (cases 8, 12, and 13) are described in detail elsewhere (Grieve, 1964; Delahunty, 1967).

The initial complaint in all was dysphagia with intense pain, the pain being most severe in the upper retrosternal area. In addition nine had a persistent retrosternal pain that in four radiated to the back. The discomfort limited most of the patients to liquid foods although some were unable to swallow anything. In addition eight patients were troubled with regurgitation and vomiting. Although oral thrush was seen in 11 of the 13 cases, in most it was mild.

The diagnosis was confirmed radiologically by barium swallow in nine instances (cases 1, 3, 4, 5, 7, 8, 10, 12, and 13). Figure 1 illustrates the radiographic appearance of the oesophagus in case 4 and demonstrates the characteristic shaggy and irregular outline of the barium column with loss of mucosal folds. X-ray examination failed to confirm the diagnosis in one patient (case 11) 10 days

after the onset of symptoms, in whom severe oesophageal candidiasis was found at necropsy two weeks later. The diagnosis was not made until necropsy in two other patients (cases 2 and 6). In one patient (case 9) the diagnosis was made at oesophagoscopy by biopsy. In three patients (cases 1, 10, and 13) the radiological appearance of the oesophagus on barium swallow was the only evidence for the diagnosis which must therefore remain presumptive. However, in two the radiograph became normal after treatment with Nystatin. The organism was identified in eight cases, seven being *C. albicans* and one *C. kruzei*.

Six of the patients (cases 1, 2, 3, 4, 5, and 6) had a grave blood disease associated with neutropenia. It is of note that these six were the same six patients who had been receiving corticosteroids before the onset of symptoms and include four of the five who had been treated with antibiotics.

Of the seven patients without haematological disease only one (case 11) had received antibiotics during the six months beforehand. None had received corticosteroids. One patient (case 8) was an alcoholic, one (case 9) had a benign oesophageal stricture, and one (case 7) had Parkinson's disease. Three patients had been well until the onset of symptoms, although one of them (case 12) was in her ninetieth year.

Plasma proteins were examined in five patients (cases 1, 2, 4, 5, and 7); none of them had hypogammaglobulinaemia. The precipitin test for *C. albicans* was positive in two instances (cases 6 and 7).

All the patients were treated with Nystatin although in three patients in whom the diagnosis had not been made in life, it was prescribed for oral thrush. The oesophagitis was cured in six patients; in five this was confirmed radiologically by barium swallow and in one by oeso-

FIG. 1. Barium-swallow (case 4). The outline of the barium column in the upper two-thirds of the oesophagus was irregular and ragged, and the mucosal folds were lost.

TABLE I

CLINICAL DETAILS OF 13 PATIENTS WITH OESOPHAGEAL CANDIDIASIS

Case No.	Age	Sex	Underlying Diagnosis	Oral Thrush	Pain on Swallowing	Vomiting and Regurgitation	Chest Pain	Pain Referred to Back	Barium Swallow	Oesophagoscopy	Result of Treatment	Survival
1	67	F	Aplastic anaemia	+	+	0	0	0	Diagnostic	—	Cure confirmed radiologically	Alive
2	52	F	Aplastic anaemia	+	+	+	+	+	Not done	—	No improvement	2 weeks
3	33	F	Aplastic anaemia	+	+	+	0	0	Diagnostic	—	No improvement	7 days
4	53	M	Pancytopenia due to disseminated tuberculosis	+	+	0	+	0	Diagnostic	—	No improvement	7 days
5	53	F	Acute leukaemia	+	+	+	+	+	Diagnostic	—	No improvement	4 weeks
6	47	F	Acute leukaemia	+	+	+	+	+	Not done	—	No improvement	2 weeks
7	64	M	Parkinson's disease	+	+	+	+	0	Diagnostic	—	Cure confirmed radiologically	Alive
8	53	F	Alcoholism	0	+	0	0	0	Diagnostic	Oesophageal candidiasis	Cure confirmed radiologically	Alive
9	86	M	Peptic oesophageal stricture	0	+	+	+	0	Not done	Oesophageal candidiasis confirmed by biopsy	Cure confirmed radiologically	>4½ years
10	61	F	None ^a	+	+	+	+	0	Diagnostic	—	Improved	2 weeks
11	57	F	Subacute bacterial endocarditis	+	+	0	0	+	Normal	—	No improvement	4 weeks
12	89	F	None	+	+	+	+	0	Diagnostic	—	Cure confirmed radiologically	Died 6 months later of pneumonia
13	53	F	None	+	+	0	+	0	Diagnostic	—	Cure confirmed radiologically	Alive

^aReceived short course of tetracycline 8 months previously ^aAlso received 6-mercaptopurine ^aPossibility of coexisting oesophageal carcinoma not ruled out

phagoscopy. The symptoms in a seventh patient (case 10), who died two weeks later, improved but there was no necropsy.

DISCUSSION

Many authors believe that *Candida* infection has only become common in recent years and have attributed this to the introduction of antibiotics (Drouhet, 1957; Louria, Stiff, and Bennett, 1962; Seelig, 1966a and b). However, candidiasis was undoubtedly common in the last century, and deaths due to candidiasis in England and Wales did not increase between 1940 and 1964 (Winner and

Hurley, 1964; Registrar General, 1967). There is some experimental evidence to suggest that tetracycline enhances the growth of *Candida* by altering host resistance (Seligmann, 1953). Nevertheless Robinson (1954) found no increase in the incidence of *Candida albicans* in cultures from faeces, vagina, and throat when a group of patients who had been taking tetracycline or penicillin for two to four weeks were compared with a similar group who had received no antibiotics.

Most reports of oesophageal candidiasis concern patients who had been receiving antibiotics, therefore eight of the patients described here are exceptional. One of our patients received a course of

TABLE I—continued

Necropsy	Organism	Blood Count at Onset of Symptoms			Antibiotics	Corticosteroids
		Hb (g%)	WBC per cmm	Neutrophils per cmm		
—	Not identified	8.3	2,200	88	None	Prednisolone 60 mg daily for 2 weeks before the onset of symptoms
Candida oesophagitis	Not identified	4.0	300	114	None	Prednisolone 10-20 mg daily for 2 years before the onset of symptoms
Candida oesophagitis	<i>C. albicans</i>	10.3	700	14	Ampicillin for 1 week ending 1 week before onset of symptoms	Prednisolone 40 mg daily for 10 days before the onset of symptoms
Candida oesophagitis	<i>C. albicans</i>	12.4	750	465	Streptomycin and INAH for 2 months ending 1 month before onset of symptoms	Prednisolone 40 mg daily for 3 weeks, 3 months before the onset of symptoms
Candida oesophagitis	<i>C. albicans</i>	5.2	55,000	0	Ampicillin by mouth for 4 days, 2 weeks before onset of symptoms	Prednisolone 40 mg daily for the 10 days before the onset of symptoms
Candida oesophagitis	<i>C. albicans</i>	6.9	89,000	1,780	Tetracycline by mouth for 1 week 6 weeks before onset of symptoms, subsequently ampicillin for 1 week	Prednisolone 40 mg daily for the 6 weeks* before the onset of symptoms
—	<i>C. albicans</i>	15.4	17,600	Leucocytosis on film	None	None
—	<i>C. kruzei</i>	14.5	8,000	—	None	None
—	Not identified	11.7	7,700	Normal on film	None	None
Not done	Not identified	11.4	17,500	Leucocytosis on film	None	None
Candida oesophagitis	<i>C. albicans</i>	9.3	4,800	Normal on film	Penicillin intramuscularly and by mouth for the 10 days before the onset of symptoms	None
Not done	<i>C. albicans</i>	—	—	—	None	None
—	Not identified	14.0	7,700	—	None ¹	None

tetracycline for pneumonia soon after beginning treatment for oesophageal candidiasis and despite this he fully recovered.

Corticosteroid therapy is thought also to predispose to Candida infection and there is animal experimental evidence to support this idea (Louria, Fallon, and Browne, 1960). The majority of cases of oesophageal candidiasis described previously have occurred in patients receiving corticosteroids. Seven of the 13 patients described here had never received corticosteroids, and the oesophagitis in one patient with aplastic anaemia was cured with Nystatin

despite the continuation of prednisolone in a dose of 40 mg a day.

All the patients in this series who were receiving corticosteroids and all but one of those who had received antibiotics had serious disease of the blood such as aplastic anaemia or acute leukaemia. Such patients are known to be susceptible to oesophageal candidiasis (Baker, 1962; Jensen, Stenderup, Thomsen, and Bichel, 1964; Gruhn and Sanson, 1963; Prolla and Kirsner, 1964), and it is regarded as a grave complication. A study of necropsies in acute leukaemia suggested that the incidence of

mycotic infection, including *Candida*, has increased since the introduction of antibiotics (Baker, 1962). Such a conclusion may be misleading. Antibiotics, blood transfusion services, and chemotherapy have together prolonged the survival of patients with leukaemia (Roath, Israëls, and Wilkinson, 1964) and aplastic anaemia (Israëls and Wilkinson, 1961) and this extension of the period at risk in itself may be enough to give rise to a significant increase in the incidence of mycotic infection. Craig and Faber (1953) and later Baker (1962) drew attention to the profound neutropenia that is often present at the onset of mycotic infection in leukaemia and aplastic anaemia, and although special attention has not often been drawn to the white blood cell count, a number of cases of oesophageal candidiasis have occurred in association with neutropenia (Gruhn and Sanson, 1963; Andrén and Theander, 1956; Eban and Symers, 1959; Kaufmann, 1958; Kaufman and Levene, 1958; Gibson and Harris, 1967), which in the case described by Eban and Symers, as in case 4, was due to disseminated tuberculosis. Louria and Brayton (1964) have shown that human leucocytes engulf *Candida in vitro* and it may be relevant that, on reviewing the histology available from the neutropenic patients who died with oesophageal candidiasis, there was a striking lack of leucocyte infiltration into the lesions. All the patients described here who had a blood dyscrasia were neutropenic, and in five of the six (cases 1, 2, 3, 4, and 5) this was profound. Possibly leucocyte infusions would have value in the prevention and treatment of mycotic infections in these cases.

There is no specific explanation for the oesophageal candidiasis that occurred in the seven patients who did not have a blood disease. Only one had had antibiotics and none had received corticosteroids. The health of most of these patients was impaired in a variety of ways and only one was thoroughly healthy before the onset of symptoms.

The symptoms of oesophageal candidiasis are distressing. Not only is swallowing intensely painful but there is often a persistent retrosternal pain radiating into the back. Such a distribution conforms with the oesophageal pain pattern (Bernstein, Fruin, and Pacini, 1962) but it may be confused with cardiac or pericardial pain. The diagnosis can be conveniently confirmed by barium swallow, although occasionally the radiographs will be normal in patients later found to have the condition. The radiological appearances have already been well described (Andrén and Theander, 1956; Eban and Symers, 1959; Marsh, 1959; Weiss and Epstein, 1962; Buckle and Nichol, 1964; Grieve, 1964) and the shaggy and irregular outline of the oesophagus shown in Fig. 1 is characteristic of this condition.

Occasionally the radiological abnormality is confined to a segment of the oesophagus and leads to the mistaken diagnosis of carcinoma (Gibson and Harris, 1967). Progress during treatment can be assessed readily by further radiological examinations.

Hitherto *C. albicans* has been the only species identified in reported cases of oesophageal candidiasis and it was surprising that *C. kruzei*, a species rarely pathogenic to man, was isolated from case 8.

Nystatin is the drug of choice and should be given as a combined mouthwash, gargle, and swallow of 250,000 units suspended in water every two hours when symptoms are severe. In the majority of cases a course of treatment lasting many weeks is required. Amphotericin B has been used (Jensen, Stenderup, Thomsen and Bichel, 1964) but because of its toxicity should be reserved for systemic and deep seated *Candida* infection.

SUMMARY

A group of 13 patients who developed *Candida* infection of the oesophagus is described. The patients complained of difficult and painful swallowing often associated with persistent retrosternal pain. The diagnosis was confirmed radiologically in nine cases by barium-swallow examination.

Treatment with corticosteroids and antibiotics has been blamed for the infection in the majority of cases of oesophageal candidiasis reported previously, but only seven of the 13 patients described here had received these drugs. However, neutropenia may sometimes be a factor in the pathogenesis of oesophageal candidiasis and merits further consideration, since all but one of the patients who had received antibiotics and all the patients who had been treated with corticosteroids had neutropenia due to a blood disease such as aplastic anaemia or leukaemia.

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