TORULA HISTOLYTICA (CRYPTOCOCCUS NEOFORMANS) GRANULOMA OF THE LUNG TREATED BY PULMONARY RESECTION

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The Medical Research Council in 1949 recommended that the name *Cryptococcus Neoformans*, rather than its more popular synonym *Torula Histolytica*, be used. Other synonyms for this fungus are *Cryptococcus Histolyticus* and *Cryptococcus Hominis*.

Cox and Tolhurst emphasised that, although torulosis is usually a generalized disease, symptoms due to cerebral involvement usually cause the patient to seek medical attention and eventually cause death. At autopsy many organs are found to be involved. The lungs are always found to be involved at autopsy, and are nearly always found to be involved when the meningitis is detected before death.

Many cases have been described in which the lungs are apparently the only organs involved. As it is possible that the portal of entry to the body is via the air passages, it seems reasonable to resect the affected lung tissue, if practicable, before dissemination from this site occurs. Many patients with torulosis apparently localized to a lung, or portion of a lung, have had pulmonary resection performed, and some patients have been apparently cured of the disease. In some of these patients the diagnosis has been made pre-operatively by detecting torula in the sputum, bronchial washings, material obtained at aspiration biopsy of the lung mass, and tissue obtained by biopsy of an endobronchial granuloma. In others the lung lesion has been resected because the sound principle, that all undiagnosed circumscribed lesions in the lung should be resected, has been followed. Such apparently curative resections, for lesions apparently localized to the lung tissue resected, have been reported by Starr *et al.* (one case), Bonmati *et al.* (three cases), Susman (one case), Cruickshank *et al.* (one case), Geaney *et al.* (one case), and Poppe *et al.* (two cases).

Even if there is evidence of a meningeal or another systemic lesion it is probably worth while resecting a localized pulmonary lesion, for, as Gendel *et al.* have pointed out, spontaneous healing

of systemic lesions is possible. Admittedly this is most unlikely in meningeal lesions; but one patient, B.J., in our series, had proven torula meningitis when she had a segmental lung resection for a toruloma six years ago, and she is now well and has no symptoms suggestive of meningitis. Another patient in our series had a left lower lobectomy for a torula granuloma eight years ago. At the time of operation he had a spherical opacity, 1 in. in diameter, in his right upper lobe—presumably another torula lesion. This gradually became smaller, and is now represented by a scarcely detectable linear scar.

Unfortunately the reverse sometimes happens and the operation of pulmonary resection is followed by an increased rate of deterioration in other systemic lesions. Undetected and unsuspected meningitis has become perfectly obvious soon after operation—such patients have been reported by Geaney *et al.*, Cruickshank *et al.*, Fortune *et al.*, and Dormer *et al.* It is interesting to note that the meningitis in Dormer's case responded very satisfactorily to big doses of potassium iodide. Meningitis, suspected to have been present for a long time and causing few abnormal symptoms or signs, sometimes deteriorates very rapidly after operation. Bonmati *et al.* report such a case. One patient in our series, K.M., proven to have meningitis before segmental resection of his lung for torula granuloma, started to deteriorate very rapidly as far as his meningitis was concerned one month after operation. Unfortunately no drugs are effective in preventing post-operative spread or deterioration. Sulphadiazine, potassium iodide, actidione, undecylenic acid and mycostatin have all been found useless in vivo, although effective in vitro. None of our patients had any specific medical treatment except for M.J.E. who had a 14-day course of sulphadiazine which had no useful effect on his lung lesions.

Between these two extremes are patients whose extrapulmonary systemic torula lesions are not affected by lung resection. They neither spread

their disease nor activate existing extrapulmonary disease in the post-operative period. Such patients have been described by Susman and Beck *et al.*

We have treated four patients with torula granuloma of the lung by lung resection in the last eight years. In all the lung lesion was a circumscribed granuloma. We have not seen any patients with the miliary, or cavitated or bronchopneumonic lesions described. In none of the patients were drugs or hyperthermia used in the treatment of the pulmonary or extrapulmonary lesions, except M.J.E. mentioned above. In all patients torula was identified in the sputum, bronchial washings, aspiration biopsy tissue, cerebro-spinal fluid or operation specimen by its morphological appearance or cultural and animal inoculation behaviour. One patient developed an apical empyema post-operatively which healed rapidly; otherwise there were no intrathoracic post-operative complications. No patients now have residual or recurrent torula lesions demonstrable in their lungs, and no patients have torula in their sputum. No patients spread their disease to extrapulmonary sites after operation. Two patients had proven torula meningitis prior to operation, and we are grateful to Dr. E. Graeme Robertson for permission to mention these patients, as he intends to report on the neurological aspects of their disease more fully at a later date. In one of these patients, B.J., the meningitis has apparently been arrested or cured, as she has been symptom free since her operation six years ago, although a pleocytosis in the cerebro-spinal fluid persisted for some months after operation. In the other patient the meningitis started to deteriorate rapidly one month after operation, and he now appears to be slowly dying.

Case Histories

Case 1

J.R.E., an animal laboratory worker, was found to have pulmonary tuberculosis, with a positive sputum in 1942, when aged 21 years. The left lung only was involved. A left artificial pneumothorax was induced in February, 1943, and maintained for 18 months, when it was abandoned because of the development of an obliterative pleuritis. He returned to work as a laboratory assistant in 1944, five months before the artificial pneumothorax was abandoned. He was reviewed clinically and radiologically at regular intervals. His sputum remained negative for tubercle bacilli after his discharge from hospital, and he remained well until April 1949. He then complained of cough and purulent sputum of one month's duration. On examination he had an

FIG. 1.—Chest X-ray showing large torula granuloma in the left lower lobe and smaller granuloma in the upper zone of the right lung.

evening temperature of 99°F., and crepitations were heard in the left axilla. A chest X-ray showed a spherical mass, $2\frac{1}{2}$ in. in diameter in the left lower lobe posteriorly, and a mass 1 in. in diameter in the right upper lobe (Fig. 1). The lesions were regarded as tuberculomata; but his sputum was repeatedly negative for tubercle bacilli. He was given 30 g. of streptomycin; but the lesions at first increased in size, then subsequently became a little smaller. Bronchoscopy was normal. The Casoni test was negative. On June 27, 1949, an aspiration biopsy of the left lower lobe mass was performed in the operating theatre (J.I.H.). A little pus was obtained and stained immediately. *Torula histolytica* was seen, and this fungus subsequently grew on Sabouraud's medium inoculated with this pus. He was therefore given sulphadiazine, one gram four-hourly for two weeks. Neither lesion decreased in size, so, on August 11, 1949, a left lower lobectomy was performed (J.I.H.). *Torula histolytica* was seen in stained sections of the granuloma in the left lower lobe. There were no post-operative complications. The patient was mobilized gradually in hospital and sanatorium because of the previous history of pulmonary tuberculosis. He returned to his work as an animal laboratory assistant in April, 1950.

He has been reviewed regularly since then. He has remained well and working, and his sputum

FIG. 2.—Case 2 (A.R.W.). Resected left lower lobe showing torula granuloma.

has been consistently negative for tuberculosis and torula. The untreated lesion in his right upper lobe has disappeared completely. He has not developed any new opacities in either lung, and he has not developed any symptoms or signs suggestive of meningitis. Corpe *et al.* have also reported a case of pulmonary tuberculosis complicated by torulosis.

Case 2

A.R.W., a soldier aged 46, had a routine chest X-ray on August 8, 1949. A spherical shadow 1 in. in diameter was seen in the left lower lobe posteriorly. He had no abnormal symptoms, and no abnormality was found on physical examination. The Casoni test was negative, his sputum was negative for tubercle bacilli, and the bronchoscopy was normal. On September 30, 1949, a left lower lobectomy was performed (I.H.McC.). Torula was seen in the stained section of the granuloma in the resected lower lobe (Fig. 2). Clinically and radiologically he has remained perfectly well since operation.

Case 3

B.J., a married woman aged 38 years, was admitted to hospital on December 12, 1950.

FIG. 3.—Case 3 (B.J.). X-ray showing torula granuloma in the subapical region of the left upper lobe.

She complained that, for about eight years, she had been getting headaches at intervals of one to six months. These headaches were severe and lasted about three weeks. For three months prior to her admission to hospital she has been coughing up blood stained purulent sputum, and she had lost a stone in weight. For a fortnight she had noticed double vision. No abnormality was found on physical examination. The cellular and chemical changes in her cerebrospinal fluid were consistent with torula meningitis, and the fungus was grown from the cerebrospinal fluid. Her sputum contained torula which was detected by smear and culture on Sabouraud's medium. A chest X-ray showed a solid lesion in the posterior segment of the left upper lobe (Fig. 3). On January 12, 1951, the posterior segment of the left upper lobe and an adjacent extrapleural empyema were removed (J.I.H.). Post-operatively she developed an apical empyema which was healed when she was discharged from hospital on May 23, 1951.

She has been reviewed regularly by us and by Dr. E. Graeme Robertson since her discharge from hospital. She has no sputum, and her chest X-rays have remained perfectly clear. She has no neurological symptoms or signs suggestive of residual torula meningitis, although, for some time, post-operative lumbar puncture revealed a diminishing pleocytosis in the cerebrospinal fluid.

Comment

1. So far as we have been able to determine she is the only patient who has been apparently cured of torula meningitis known to be present before the torula lung lesion was resected. However, we

FIG. 4.—Case 4 (K.M.). X-ray showing torula granuloma in the right lower lobe and calcified tuberculous lesion in the right upper lobe.

realize that torula meningitis can be a very chronic disease, and therefore realize that a relapse is still possible.

2. Patients who have a chest X-ray showing a circumscribed opacity, and cerebral and meningeal symptoms are usually suspected of having carcinoma of the lung with cerebral secondaries, or pulmonary tuberculosis with tuberculous meningitis. Case 4 also was at first suspected of having pulmonary tuberculosis and tuberculous meningitis because of his pulmonary and meningeal symptoms, and particularly because his chest X-ray showed a large calcified tuberculous focus in the right upper lobe as well as the lesion in the right lower lobe. All such patients should have their sputum, bronchial washings and cerebrospinal fluid examined by smear, culture, and animal inoculation to determine whether or not they are, in fact, suffering from torulosis of the lung and meninges. We would suggest that quite often it would be reasonable to do an exploratory thoracotomy and lung resection on such patients if neither carcinoma nor tuberculosis were proven pre-operatively.

Case 4

K.M., a male aged 41, a motor truck driver, was admitted to hospital on March 6, 1957. He complained of attacks of headache and giddiness for ten years. During the six months prior to admission to hospital he had lost half a stone in weight. Eight weeks prior to his admission to hospital a routine chest X-ray was taken and this

showed a large lobulated opacity in the basal segments of the right lower lobe, and a large calcified opacity at the apex (Fig. 4). For six weeks prior to his admission to hospital he had been coughing up blood stained purulent sputum each morning. The day before his admission to hospital he had an attack of intense vertigo. No abnormality was found on physical examination. His sputum was negative for tubercle bacilli; but it contained *torula histolytica* which was clearly shown by Indian ink and Leishman stains. Bronchoscopic findings were perfectly normal; but the bronchial washings contained torula fungi which were seen in the stained specimen and which grew on Sabouraud's medium. Lumbar puncture findings were consistent with torula meningitis. No torula was seen in the stained specimen of cerebro-spinal fluid, nor did the fungus grow when the fluid was sown on Sabouraud's medium. However, a mouse was inoculated with the cerebro-spinal fluid and this test was positive for torula. On March 19, 1957, the basal segments of the right lower lobe were resected (I.H.McC.). This portion of lung contained a large lobulated mass which felt rubbery. Macroscopically it was similar to the other three resected lesions. The surface was greasy, and the outline of alveoli could be clearly seen with a hand lens. The lesion was fairly well encapsulated. Torula was seen in stained sections of the resected granuloma.

He was discharged home, free of chest and meningeal symptoms, on April 2, 1957. One month later severe cerebral symptoms developed. Vomiting, headache, vertigo, diplopia, incontinence of urine and poor memory all troubled him. Neither the physical signs nor the electroencephalogram findings suggested a localized, and therefore resectable, intracranial torula granuloma. His cerebral condition is still deteriorating, and it seems that he will not live very long.

Summary

Four cases of torula granuloma of lung, treated by pulmonary resection, are described.

In three cases the diagnosis was established pre-operatively. One patient was operated on because of an undiagnosed, circumscribed opacity in his chest X-ray.

Three of our cases, unlike most described, had symptoms referable to the chest—two had haemoptyses, and one had purulent sputum.

Two cases had torula meningitis proven prior to the lung operation. One remains well six years after operation. The meningeal condition of the other has deteriorated rapidly in the four months after operation.

One patient suffered from pulmonary torulosis complicating pulmonary tuberculosis.

Resection of a toruloma of the lung, even in the presence of torula meningitis, is justifiable.

A combination of an opacity in the chest X-ray, with or without lung symptoms, and meningitis, may not be due to pulmonary tuberculosis with tuberculous meningitis or lung carcinoma with cerebral metastases. One must realize that this combination may be due to torula granuloma of the lung with torula meningitis.

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