A MALIGNANT BRONCHIAL ADENOMA PRESENTING AS A CARCINOID SYNDROME

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Biörck *et al.*[1] first drew attention to a patient with pulmonary stenosis and tricuspid insufficiency associated with a carcinoid of the jejunum, which had metastasized to the liver. They described a peculiar cyanosis of the trunk and face and vermilion mottling induced by excitement, in this patient, a 19-year-old boy who died after angiocardiography. Thorson *et al.*[2] collected reports of similar cases. With their own,[1] there were 7 definite and 9 possible cases. The features of the syndrome were described as follows:

1. Malignant carcinoid of the small intestine with metastases to the liver.

2. Dependent oedema.

3. Frequent watery stools with borborygmi and abdominal pain.

4. Widening of the small vessels of the skin with telangiectases in some cases.

5. Pellagra-like cutaneous lesions.

6. Plethora and cyanosis with peculiar patchy flushing of the skin.

7. Pulmonary stenosis and tricuspid regurgitation.

8. Attacks of bronchial asthma.

The basis for the symptomatology of the above syndrome was thought to be serotonin (5-hydroxytryptamine), since Lembeck had isolated considerable quantities of this substance from a carcinoid tumour in 1953.[3] Early studies of serotonin activity in animals showed some of the above effects, viz. bronchoconstriction, hyperperistalsis, increased pulmonary vascular resistance, and reddening of the skin.[4] Subsequent investigation of the humoral effects of 5-hydroxytryptamine (5-HT) and the related histamine release have further elucidated the mechanism of the syndrome.[5,6]

In 1958 Dockerty *et al.*[7] first reported the occurrence of a metastasizing bronchial adenoma with the carcinoid syndrome. Twenty-one cases have now been published confirming this association,[8,9] and two cases of oat-cell carcinoma of the lung have been reported in association with the carcinoid syndrome.[10,11] A further case of malignant bronchial carcinoid giving rise to the syndrome is now presented.

CASE REPORT

History

A 57-year-old White female presented in January 1962 with a history of progressive dyspnoea and severe diarrhoea of eight weeks' duration. She passed up to 15 stools a day, and the evacuation of these stools was forceful. She complained of periodic abdominal cramps. In addition, polyarthralgia had been present intermittently for 9 months and she had noted progressive weight loss over this period. For about 15 years she had had a cough, but recently this had become more severe and was now associated with copious yellow sputum. She admitted to being a heavy smoker. She had been in hospital on 3 previous occasions during 1958 and 1959 for lung infections and congestive cardiac failure. The extent of the consolidation and atelectasis in 1958 is seen in Fig. 9A. She was maintained on therapy against cardiac failure.

Examination

Her face was florid and central cyanosis was present. The blood pressure was 120/70 mm.Hg. She was in congestive cardiac failure. The liver edge was palpable 5 cm. below the costal margin, and it was tender and firm, with an irregular surface. The spleen was just palpable. The heart was clinically slightly enlarged, with neither side predominant. A right atrial

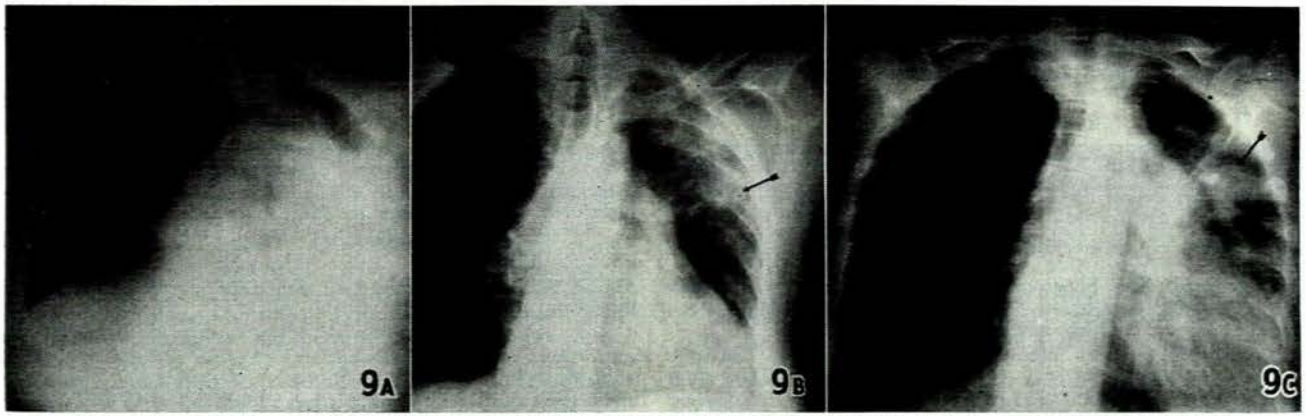


Fig. 9 A. Consolidation and atelectasis in 1958. *B.* Irregular, rounded opacity in left upper lobe. *C.* Close-up of same lesion as in B.

gallop was heard, a systolic murmur suggestive of tricuspid incompetence was present, and there was a grade-II pulmonary ejection systolic murmur. Bronchospasm was evident throughout both lung fields, and signs suggestive of localized infection were elicited at the right base and the left apex.

Investigations

The blood picture was normal and the erythrocyte sedimentation rate was 8 mm. in one hour (Wintrobe).

Liver-function tests and serum-protein electrophoresis were essentially normal.

No pathogens were present in the stools and the fat content was normal.

The augmented histamine test showed hyperchlorhydria (free HCl 115 mEq./l., total acid 125 mEq./l).

The electrocardiogram showed no significant abnormality.

Chest X-ray showed cardiomegaly and prominence of the pulmonary outflow tract. The mediastinum was displaced to the left, presumably following on the fibrosis associated with the previous left-sided pneumonia. Loss of translucency at the right base and left apex was present. A poorly-defined, irregular, rounded opacity was seen in the left upper lobe (Figs. 9B and 9C). Full radiological investigation of the gastro-intestinal tract was negative.

Progress

The chest infection improved on penicillin, but the cardiac failure was slow to respond, and the diarrhoea was resistant, to standard therapy. Over a six-week period, the clinical features of the carcinoid syndrome emerged. A violaceous mottling of the upper limbs and the head and neck became evident. This varied in intensity, and was not affected by oxygen administration. Telangiectatic vessels were noted on the hands and the face. The hepatomegaly increased and the surface of the liver was now clearly hard and nodular. Bronchospasm and sweating occurred intermittently. Urinary 5-hydroxy-indole-acetic acid (5-HIAA) was elevated to 62 mg. per 24 hours (normal 2-14 mg. per 24 hours), and the diagnosis of a carcinoid syndrome was proved by liver biopsy, which showed the presence of metastatic carcinoid.

The shadow in the left upper lobe, taken together with the absence of any obvious lesion in the bowel, suggested a possible primary bronchial carcinoid.

Management

The obviously diffuse hepatic metastases precluded operation, and radiotherapy has not been of benefit in other cases.[12] Alleviation of the symptoms became the primary aim. The potent serotonin antagonist, 1-methyl-D-lysergic acid butanolamide ('deseril') was given orally in divided doses (8 mg. per day). The hyperperistalsis, and consequently the diarrhoea, responded in a striking fashion (Fig. 10).

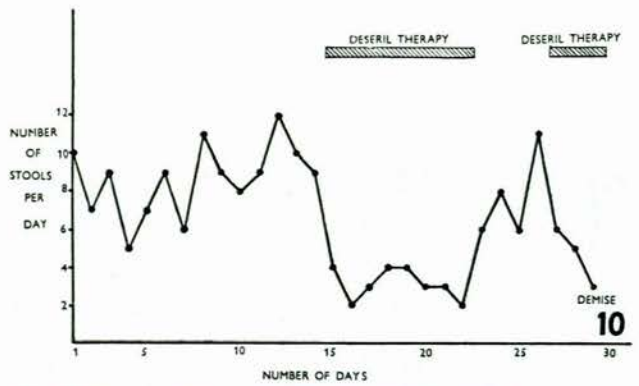


Fig. 10. Dramatic response of diarrhoea to deseril therapy.

Despite this control of the hyperperistalsis, the downhill course was progressive and the patient died nine weeks after admission. The terminal collapse was heralded by tremendous vermilion flushing, sweating and bronchospasm.

AUTOPSY REPORT

The postmortem examination was carried out 40 hours after death, and the relevant findings were as follows:

Marked adhesions were present between the parietal and visceral layers of the pleura on the left side of the thorax. Adhesions were also noted between the parietal and visceral layers of the pericardium. On section of the left lung an irregular white tumour, measuring approximately 5 cm. across, was found in the upper lobe. The site of origin was traced to an upper-lobe bronchus. The tumour appeared to be infiltrating the surrounding parenchymal tissue and the hilar nodes were also infiltrated. The right lung showed no significant pathological change. The left and right ventricles were slightly dilated. No valvular lesions were found on either side of the heart, and no endocardial lesion was present.

No fibrous-tissue plaques were found in the major vessels. No tumour of the bowel was present, and there was no evidence of peptic ulceration. The liver weighed 2,500 G. and was firm and irregular. It was widely infiltrated by metastatic tumour. The gallbladder contained a few mixed stones, but the mucosa showed no significant pathological change. The glands of the porta hepatis were infiltrated. The pancreas was normal.

The kidneys showed macroscopic evidence of focal chronic pyelonephritis. A metastatic nodule was present in the left adrenal gland.

The right lobe of the thyroid gland was haemorrhagic and appeared to be infiltrated by tumour.

HISTOLOGY

(*See colour plate on opposite page*)

Lung

The tumour had widely infiltrated the upper lobe of the left lung and had invaded the parenchymal tissue. The cells were fairly uniform in size with relatively small nuclei, but in many areas this uniformity was lost and frankly anaplastic cells were present. These anaplastic cells had large pyknotic nuclei, and mitotic figures were not uncommon (Figs. 2 and 3). The tumour cells were arranged either in distinct alveolar pattern or in sheets, often running irregularly along a basement membrane.

In the region of the glands there appeared to be a definite transformation from normal bronchial glandular epithelium to the carcinoid cell. The nuclei in these regions

Fig. 1. Note the transition from normal glandular cells, with cytoplasm staining a bright magenta, to tumour cells with altered staining properties. Groups of carcinoid cells can be seen below and to the right of centre and in the left-hand corner (periodic-acid Schiff technique × 180).

Fig. 2. Frankly malignant carcinoid cells forming crude alveolar patterns. A single PAS-positive cell can be seen on the upper right (periodic-acid Schiff technique × 740).

Fig. 3. Malignant carcinoid cells in an alveolus. Note the intact myo-epithelial cells (periodic-acid Schiff technique × 1,800).

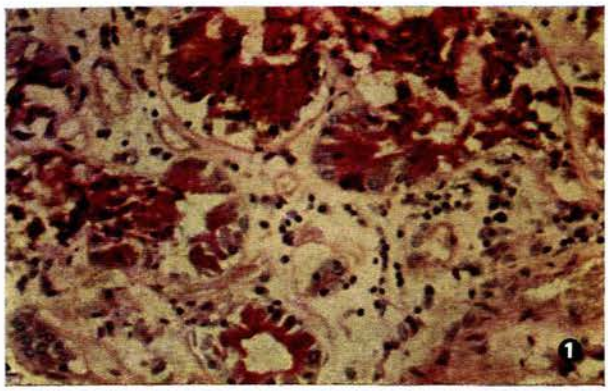
Fig. 4. Carcinoid cells with granules of argyrophil material (Bodian silver impregnation method × 1,800).

Fig. 5. Well-marked fibrous-tissue reaction in the lung. Isolated groups of carcinoid cells with dark nuclei and pale cytoplasm can be seen in and around the proliferating fibroblasts (Masson trichrome × 180).

Fig. 6. Metastatic carcinoid in the liver (haematoxylin and eosin × 180).

Fig. 7. Encapsulated metastatic carcinoid in the adrenal gland (haematoxylin and eosin × 180).

Fig. 8. Invasion of the thyroid by metastatic tumour. The tumour is seen at the lower left. Thyroid follicles are filled with pale-pink colloid or with blood. The tissue at the upper right is hyalinized fibrous tissue and unrelated to the tumour (haematoxylin and eosin × 45).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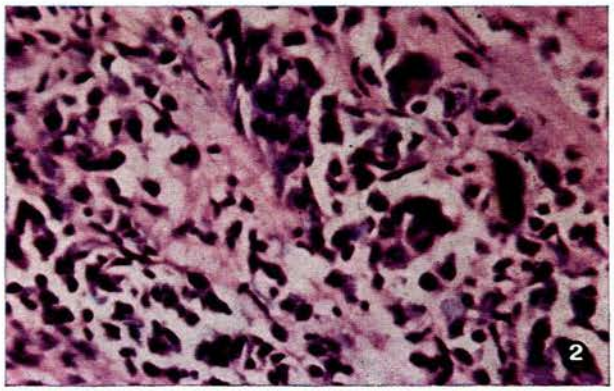
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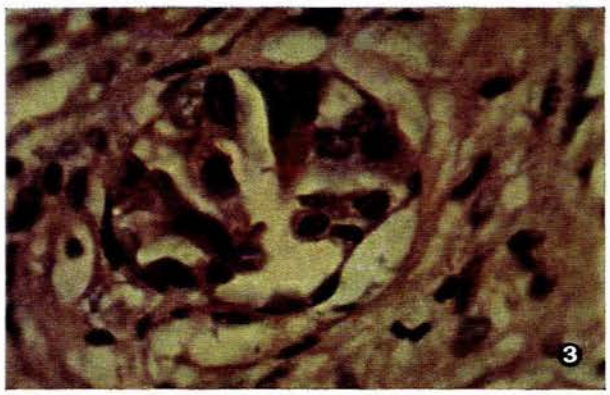
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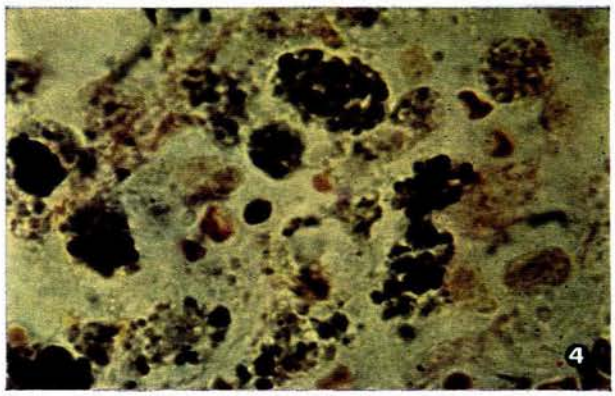
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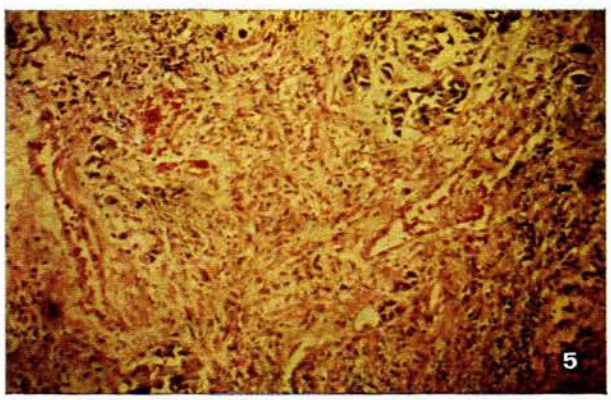
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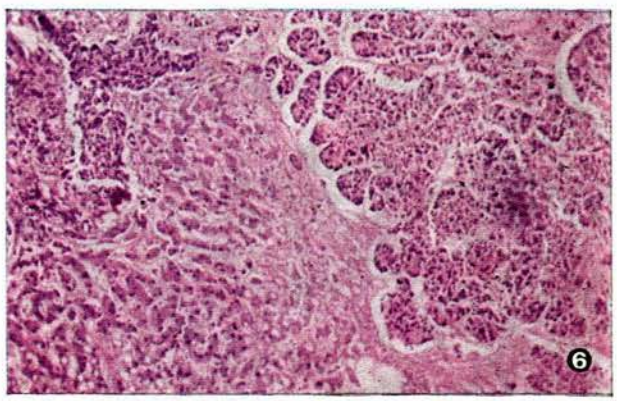
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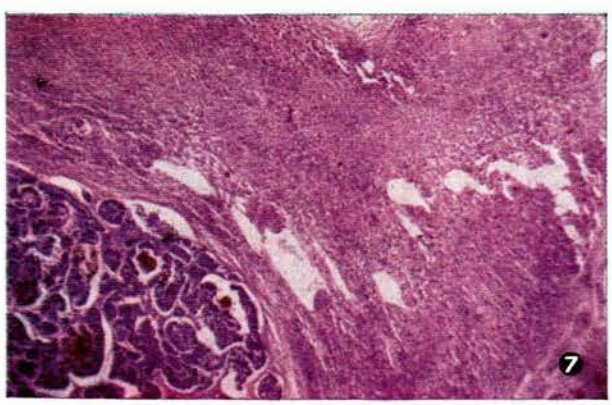
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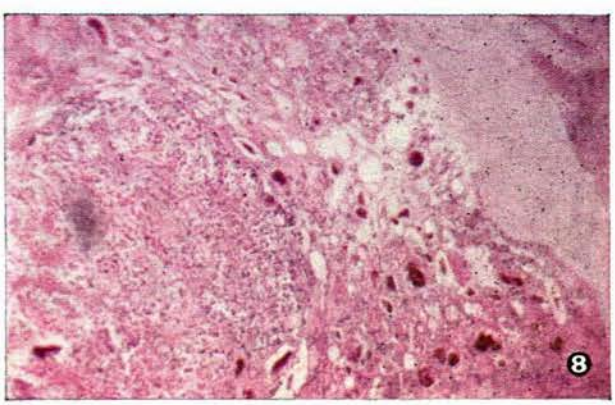
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were larger and there was a change in the staining properties of the cytoplasm (Fig. 1). In some places the tumour cells replaced the normal epithelium and grew from an intact basement membrane (Fig. 3).

Using the periodic-acid Schiff (PAS) technique, and the alcian blue stain, a transition from PAS-positive, alcian-blue-positive cytoplasm, to a negative-staining cell was observed (Figs. 1 - 3).

The argentaffin reaction (Masson-Fontana method) was negative, but silver impregnation with exogenous reduction (Bodian method) gave a positive argyrophil reaction (Fig. 4). The diazonium, Gibbs, and indophenol reactions[13] were all negative, as was the ferric-ferricyanide reduction method.

In focal areas, a well-marked fibroblastic proliferation was noted, associated with nests of tumour cells, and forming broad bands of fibrous tissue (Fig. 5). One other feature worthy of mention was the presence of a small, healed tuberculous scar containing hyaline tissue and typical cholesterol clefts.

Liver

The metastatic deposits in the liver showed essentially the same cellular patterns as were found in the lung (Fig. 6). Again a well-marked fibrosis was present in scattered areas surrounding groups of tumour cells.

Adrenals

The left adrenal gland was the seat of a well-encapsulated secondary nodule (Fig. 7).

Gastro-intestinal Tract

No significant pathological changes were found in the sections of the ileum, colon, rectum or appendix examined histologically.

Thyroid

The thyroid gland was infiltrated by tumour. The cells here were irregularly arranged and the infiltration was associated with haemorrhage and necrosis (Fig. 8).

A Review of the Liver Biopsy

The liver showed the presence of a metastatic carcinoid tumour. The argentaffin and diazonium reactions were negative. However, the argyrophil reaction was strongly positive, indicating that this was an argyrophil carcinoid from the outset.

DISCUSSION

The Histogenesis of the Carcinoid Tumour

In the case presented, there appears to be a definite transition from PAS-positive, mucin-secreting, glandular epithelium to the PAS-negative, argyrophil cell. The neoplastic cells spread from the region of the bronchial glands to invade the surrounding lung tissue, forming crude alveoli as they do so. These features support the theory that the carcinoid adenoma arises from bronchial glandular epithelium.[14]

There are two major types of bronchial adenomas, viz. the cylindromatous (or salivary) type and the carcinoid type.[15] Since the bronchial glands are a salivary type of gland, and the cylindromatous adenoma closely resembles a salivary-gland tumour, it is readily accepted that the cylindromatous adenoma in fact arises from the bronchial glandular epithelium.[16,17] On the other hand, because argentaffin cells are difficult to demonstrate in normal bronchial epithelium, the origin of the carcinoid adenoma is less obvious.

Popoff[18] demonstrated that in mucus-secreting gastric cells the argentaffin granules are a stage in the growing cell, thus presenting the possibility that argentaffin cells may be found in any mucous epithelium at a particular phase of regeneration; more recently argentaffin cells have in fact been demonstrated in the salivary glands of dogs.[19]

The cell type of most bronchial carcinoids * is argyrophil rather than argentaffin and, therefore, the argyrophil cell is of interest. This cell is more widely distributed than the argentaffin cell and has been observed in bronchi and in salivary glands.[20] Unlike the argentaffin cell, the argyrophil cell has no endogenous factor that will reduce silver. It is possible that the argyrophil cell is the precursor of the argentaffin cell.[21]

The above evidence suggests that the bronchial carcinoid adenoma, like the bronchial salivary-gland adenoma, arises from the glandular epithelium.

Pathogenesis

The carcinoid of the gastro-intestinal tract appears to be a slow-growing tumour. Metastases are not often associated with the appendiceal carcinoids.[22] Doubt, however, has been thrown on the benign nature of the bronchial carcinoid by Goodner *et al.*,[23] who pointed out that these tumours tend to metastasize readily. Out of 20 bronchial carcinoids associated with the syndrome which we were able to analyse, only 2 showed no evidence of metastases. A further 2 examples of the syndrome, caused by oat-cell carcinomas with metastases, were described.[10,11] In these 22 cases the common metastatic sites were: liver (20), hilar glands (19), bone (6), adrenal (6) and pancreas (4). Metastases to the thyroid have not previously been described in the bronchial carcinoid syndrome.

The adhesions between the parietal and visceral layers of the pleura at the site of the tumour call for brief comment. Becker drew attention to the pathognomonic kinking of the bowel from adhesions in gastro-intestinal carcinoids.[24] In other cases the fibrosis had been noted and it has been suggested that the association of fibrous-tissue proliferation at or near the site of the tumour may be a serotonin effect.[25]

In the case reported here, in addition to the macroscopic adhesions, there was histological evidence of marked fibrosis, demonstrating this local serotonin effect.

The Clinical Features

The carcinoid syndrome manifests either when the principal sites of detoxification of 5-HT and 5-hydroxytryptophan (5-HTP) have been bypassed,[12] or when the serum levels of the hormones are high. The detoxification takes place mainly in the liver and lung by amino-oxidase activity. A bypass occurs when functional secondary deposits are present in the liver, with secretion into the hepatic venous drainage, or when the primary tumour secretes directly into the systemic circulation, as when an ovarian teratoma gives rise to the carcinoid syndrome. The bronchial carcinoid secretes into the pulmonary venous

* As in our case.

system so that the pulmonary bed is bypassed to a large extent. This explains the findings in the case of Bernheimer *et al.*,[26] in which a bronchial adenoma with no distant metastases gave rise to fibrosis of the valves of the left side of the heart, instead of the usual right-sided valvular involvement seen when hepatic metastases secrete serotonin into the systemic venous system.

In Table I an analysis of the main clinical features in 22 cases of the bronchial carcinoid syndrome are set out.[7-11,15,26-27] This includes the cases involving oat-cell

TABLE I. FREQUENCY OF COMMON SYMPTOMS AND SIGNS IN 22 CASES OF BRONCHIAL CARCINOID

Symptom or sign	*No. of cases in which present*
Flushing attacks	17
Diarrhoea	16
Violaceous hue of skin	11
Bronchospasm	9
Oedema	9
Right-sided heart murmurs	7
Weight loss	7
Telangiectasia	6
Excessive sweating	6
Peptic ulceration	5

neoplasms and our own case, which demonstrates the symptoms and signs listed, with the exception of flushing attacks and peptic ulceration. However, hyperchlorhydria was present.

The valvular lesions are late manifestations,[12] which may explain the absence of fibrous-tissue lesions in the valves or in the vessels.[25] The murmurs must, therefore, have been functional in type.

The age of onset of the ileal carcinoid syndrome is between 50 and 60 years and the sex incidence is equal.[22] The bronchial adenoma presenting as the carcinoid syndrome has the same age onset (mean 53 years, range 51 - 72 years), but the sex ratio in the small number of cases reported shows a female preponderance (16 females to 6 males). This is in keeping with the female preponderance of bronchial adenomas in general.[38]

The features directing attention to the primary bronchial carcinoid as opposed to the primary gastro-intestinal tumour are the pulmonary symptoms and signs, and also osteoblastic bone secondaries when present, since these are more commonly associated with the bronchial tumour.[9,36]

Prognosis and Treatment

Although the progression is slow, the ultimate prognosis is poor. The mean survival time for the carcinoid syndrome of bronchial origin is approximately 5 years in the reported cases.

Surgical removal of a bronchial adenoma is the obvious treatment in early cases where secondary spread has not occurred. However, even metastases have been surgically excised to alleviate the symptoms.[12,39] Radiotherapy has not proved to be effective in controlling spread or the functional effects of this tumour.[12]

The control of the troublesome symptoms is therefore of primary importance in the treatment of the established syndrome. The earlier serotonin antagonists, such as D-lysergic acid diethylamide (LSD 25), had untoward side-effects. 1-methyl-D-lysergic acid butanolamide (deseril) is, however, effective in controlling the diarrhoea,[33,40,41] as in this case, and a beneficial effect on the flushing has been reported in some cases.[33,40]

SUMMARY

A case of metastasizing bronchial adenoma, presenting as the carcinoid syndrome, is described. The clinical features, the management, the histogenesis and the pathogenesis of the tumour are discussed in relation to other case reports.

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