Adrenocortical hyperactivity with disseminated malacoplakia

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SUMMARY A case is described of an ectopic ACTH syndrome associated with malacoplakia.

Numerous cases of the tumour-induced ectopic ACTH syndrome have been recorded. In the present case, a metastasising bronchial carcinoid was found to contain large quantities of an ACTH-like substance and was associated with bilateral adrenal hyperplasia. Uniquely, there was also a disseminated extravascular malacoplakia. This presented diagnostic and therapeutic problems. Malacoplakia has not been previously described in association with adrenocortical hyperactivity.

Clinical findings

The patient was a 61-year-old ragman admitted to hospital in September 1973. He complained of 'lightness of his head' for several weeks with dizziness and ataxia. He had had intermittent pain in the abdomen and right thigh for the same period.

Clinical examination revealed a plethoric face with increased skin pigmentation over the body and arms, especially in the palmar creases. There was a tender, hard, fixed swelling (5 cm in diameter) on the left side of the neck which he stated had been present for three years, fluctuating in size. There were signs of a right-sided bronchopneumonia and there was a diffuse tender swelling palpable in the right side of the abdomen. There was a discharging sinus from an enlarged firm right testis but the prostate was of normal consistency.

A chest x-ray initially showed patchy consolidation in the right lung field with pleural thickening at the right costophrenic angle. An abdominal x-ray showed a diffuse soft tissue mass displacing the caecum medially and extending into the perinephric space. A barium enema confirmed the presence of a large retroperitoneal mass of uncertain aetiology.

The pituitary fossa was not enlarged or eroded. Adrenal tomography revealed bilateral enlargement

of the adrenal glands in keeping with bilateral hyperplasia.

Surgical operations

Exploration of the right testicle revealed a hard, slightly enlarged organ with an indurated spermatic cord and a sinus to the scrotal skin; right orchidectomy was performed.

Exploration of the large retroperitoneal mass revealed a 500 ml collection of pus. This was drained but a large retroperitoneal sinus persisted. In February 1974, the patient developed a swelling in the left flank; 600 ml of pus was drained from an abscess on the left side (Fig. 1). Culture of pus from both of these abscesses repeatedly grew coliform organisms. There was no evidence of acid-fast bacilli on direct examination or on culture.

Course and management

The diagnosis of bilateral adrenal hyperplasia (Cushing's syndrome) was confirmed by the biochemical finding of elevated urinary free cortisol excretion (199 mg/24 hours), elevation of morning (9.00 am) and evening (11.00 pm) plasma 11-OHCS (19.5 mg/100 ml and 19.5 mg/100 ml respectively) and of plasma ACTH (270 pg/ml and 150 pg/ml respectively), with loss of the usual circadian rhythm.

It was felt that the patient had a primary ACTH secreting neoplasm and that the neck tumour was secondary to this but he refused any further anti-adrenal therapy. Subsequent chest x-rays suggested a small lesion in the right lung hilum. He died seven months after admission.

Histopathological findings

A biopsy of the neck lump contained a small fragment of fibrofatty tissue infiltrated at one edge by

Fig. 1 Singoram showing bilateral retroperitoneal sinuses and abscess cavities.

clumps of tumour cells. These cells were dedifferentiated and, although the appearances were in keeping with a secondary carcinoma, no definite conclusion as to the primary site could be drawn.

The right testis weighed 50 g (Fig. 2). There was enlargement of the body and replacement of the normal seminiferous tissue by a yellowish/brown mass measuring 5×4 cm on section. Histologically the testis showed sheets of cells which had abundant pink foamy cytoplasm and small, dark, eccentrically placed nuclei. Close examination of these cells revealed the presence in many of basophilic intracytoplasmic inclusions. These inclusions were uniform in size and circular in shape and were surrounded by a clear zone imparting an overall 'birds-eye' appearance (Fig. 3). Several such bodies were also noted lying in extracellular positions. Special stains revealed the presence of both iron and calcium salts in these bodies. The overall appearances were, therefore, those of Michaelis-Gutmann bodies in malacoplakia. There was no similarity between the cervical and the testicular lesions.

Relevant necropsy findings

The wall of the right upper lobe bronchus was thickened at its origin by pale, firm tumour and there was a related 1 cm diameter lymph node also

Fig. 2 Right testis partially replaced by malacoplakia. Sinus orifice is arrowed.

Fig. 3 *Malacoplakia of right testis. Typical Michaelis-Gutmann bodies are arrowed ($\times 340$).*

Fig. 4 *Point of origin of bronchial carcinoid. Note regularity of cell size and shape ($\times 100$).*

infiltrated by tumour. Histologically this showed the features of a carcinoid of bronchial origin (Fig. 4). In the left side of the neck there was a 4 cm diameter mass of tumour intimately related to, but not invading the left internal jugular vein. Histologically this was identical in appearance with the bronchial primary lesion (Fig. 5).

In each retrorenal area there was a large abscess cavity which communicated through the lateral abdominal wall bilaterally to the skin surface in a complex sinus system. Each postrenal abscess extended laterally behind the adrenals and on the right side extended up behind the right lobe of the liver. On the left side there was abscess formation in the retrosplenic region. Each abscess cavity contained thick greenish pus. In the left kidney at the superior pole there was a 2 cm diameter lesion which contained thick creamy material and was bounded by a thick fibrous wall (Fig. 6). This lesion appeared to have penetrated the capsule of the kidney and extended into communication with the left perirenal abscess.

The urinary bladder was of average size. Its wall showed a very minimal amount of trabeculation and no focal nodular lesions were seen. The prostate was of average size and to the naked eye revealed no obvious abnormality.

The right lobe of the liver contained a 4 cm diameter secondary tumour deposit.

Histologically the kidneys showed the features of chronic pyelonephritis. In one field, a small secondary deposit from the bronchial tumour was seen within a Bowman's space. In the left kidney the lesion shown in Fig. 6 was lined with malacoplakia cells. In the prostate a focus of malacoplakia was also seen microscopically.

The retrorenal abscesses and sinus tracts were studied extensively. In all sections there was an acute on chronic inflammation with vascular granulation tissue. However, in many areas the walls of the sinus tracts and the abscesses were lined by sheets of malacoplakia cells.

The pituitary was normal. Both adrenal glands showed a marked degree of hyperplasia. The left

Fig. 5 Microscopic appearance of neck mass. There are islands of small regular cells identical with those of the bronchial carcinoid ($\times 200$).

Fig. 6 Deposit of malacoplakia at the superior pole of the left kidney (arrowed).

gland weighed 15 g and the right 12.5 g (mean normal combined weight in the age-range of 61-70 years is 12.6 g) (Sloper, 1966).

Biochemical assay

Portions of the tumour in the neck region and the large secondary deposit in the liver were assayed for their content of ACTH. The neck tumour contained 0.20 mg/g of wet tissue. (This compared with a value of 6.25 pg/g of tissue obtained from a functioning basophil of the pituitary gland in another patient with classical Cushing's disease.)

Discussion

This case presented clinically with features of Cushing's syndrome. This was supported by the biochemical investigations. The patient had a mass in the left side of the neck and at necropsy the primary site of this lesion was found in the right upper lobe bronchus. Secondary deposits from this tumour were found in several sites. Assay of the tumour showed a high content of ACTH.

The ectopic ACTH syndrome is the best documented model of ectopic hormone production, and at least 94 cases with positive tumour levels by bioassay or radioimmunoassay have been published (Rees and Ratcliffe, 1974).

The amount of ACTH determined by radioimmunoassay in this present tumour was in the mid-

range of ACTH content in reported cases of ectopic ACTH production by all types of tumour tissue (0.001 to 1000 mg/g net weight). This very wide range is confirmed for both bioassay and radioimmunoassay techniques, and probably represents wide variation in peptide structure of ACTH-like compounds.

Malacoplakia was originally described by Michaelis and Gutmann in 1902. This disease was originally described in the urinary bladder and is associated with long-standing urinary infection (Morison, 1944). Malacoplakia has been described in extravesical sites such as (a) kidneys, pelvis, and ureters, by McDonald and Sewell (1914); (b) testis, by Haukoja and Chinchinian (1958), Blackwell and Finlay-Jones (1959), and Brown and Smith (1967); (c) prostate, by Hoffmann and Garrido (1964) and Coup (1976); and (d) colon, by Finlay-Jones *et al.* (1968).

The present case is unusual in that the lesion was disseminated and the urinary bladder was free of disease. Malacoplakia is characterised by the presence of large cells with abundant, eosinophilic cytoplasm. In the cytoplasm there are typical inclusions (Michaelis-Gutmann bodies). These are the approximate size of a nucleus. They stain positively with haematoxylin and eosin and special stains reveal the presence of calcium and iron salts. Frequently they have a laminated appearance. The aetiology of malacoplakia is mysterious. Michaelis and Gutmann (1902) considered it to be neoplastic. However, disseminated disease is exceptionally rare and the disease

is not now thought to be neoplastic. Several other suggested aetiological factors include tuberculosis (Curtis *et al.*, 1961), sarcoidosis, or a fungal infection. There is, however, no good evidence to support these theories. Smith (1965) was unable to demonstrate viral bodies.

Recent electron microscopic evidence (McClurg *et al.*, 1973) suggests that the inclusions represent the ingestion and persistence of bacilliform structures in macrophages. They therefore represent the end products of a persistent intracellular bacterial infection. In the present case the patient's wound sinuses persistently discharged coliform organisms and the walls of the sinus tracts contained malacoplakia cells. One can only speculate on the basis of altered reactivity by macrophages which allows persistent infection and it may be that adrenocortical overactivity contributed not only to the occurrence of malacoplakia in this case but to its widespread distribution.

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