that liver-type ALP was produced in a patient with meningioma, but they did not find an abnormal ALP value. In addition, we did not find abnormal ALP values in 100 patients with non-neoplastic intracranial diseases. Taken together, our data suggest that the abnormal ALP found in the cerebrospinal fluid from this patient was liver-type ALP produced by intracranial cancer cells which had metastasised from an alveolar lung adenocarcinoma.

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Cholecystitis, cholelithiasis, and ganglioneuromatosis of the gall bladder: an unusual presentation of MEN type 2b

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Abstract

A 40 year old man with multiple endocrine neoplasia type 2b (MEN 2b) presented with cholecystitis caused by gall stones. Twenty four years earlier, he had had a partial thyroidectomy for a cold nodule. At his initial presentation MEN 2b with medullary carcinoma of the thyroid had not been made. This was diagnosed while investigating his gall bladder symptoms and he was found to have asymptomatic residual medullary thyroid carcinoma and bilateral adrenal pheochromocytomas. The cholecystectomy specimen contained several mixed calculi and extensive ganglioneuromatosis with large, prominent nerves containing ganglion cells in the gall bladder wall.

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Neuronal hyperplasia or ganglioneuromatosis are well recognised components of multiple endocrine neoplasia type 2b (MEN 2b)^{1,2} and neurofibromatosis.³ Ganglioneuromatosis of the gastrointestinal tract often precedes the appearance of medullary thyroid carcinoma and pheochromocytoma in MEN 2b.⁴ Within the context of MEN 2b, presentation

related to gall bladder disease is rare. A case of MEN 2b is presented in which the patient complained primarily of symptoms related to gall bladder disease.

Case report

The patient was a 40 year old man who at the age of 16 years had had a partial thyroidectomy for a cold nodule. This was interpreted to be a Hürthle cell carcinoma at the time. Twenty four years later, he complained of right upper quadrant pain, dyspepsia, and flatulence. Examination showed him to be hypertensive (although he did not complain of hypertension) and to have right upper quadrant tenderness. He was also noted to have a lump in his residual thyroid and bilateral loin masses. A computed tomogram revealed an enlarged gall bladder filled with calculi, a tumour in the residual thyroid, and bilateral adrenal medullary tumours. Subsequent examination showed mucosal neuroomas of the lips, tongue, larynx and cornea. Furthermore, the patient was noted to have a marfanoid feature. MEN 2b was diagnosed and a detailed review of the patient's history disclosed a positive family history with the patient's mother having bilateral pheochro-

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Figure 1 Gall bladder wall thickened by large nerves with a plexiform pattern. The surface mucosa is intact and there is mild chronic cholecystitis (haematoxylin and eosin).

mocytomas. A brother has a similar appearance to the patient and has been treated for hypertension, presumably related to pheochromocytomas. None of the patient's children had any signs or symptoms of MEN. Serum calcitonin and urinary catecholamine values were increased. The residual thyroid was resected and bilateral adrenalectomy and cholecystectomy were performed. One year later, the patient had symptoms attributable to diverticular disease and a neurogenic bladder.

Methods

All specimens were fixed in 10% buffered formalin and processed routinely. In addition to haematoxylin and eosin stains, immunohistochemistry was performed using the streptavidin-biotin complex on formalin fixed, paraffin wax embedded tissue for the following antibodies: chromogranin (Boehringer Mannheim, Germany, dilution 1 in 100); synaptophysin (Biogenix Medos, Australia, 1 in 200); S-100 protein (Dakopatts, USA, 1 in 400); neurofilament (Dako, 1 in 50); vasoactive intestinal peptide (VIP) (Biogenix Medos, Australia, prediluted); somatostatin (Dako, 1 in 300) and glial fibrillary acidic protein (GFAP) (Dako, 1 in 150).

Pathological findings

Macroscopically, the gall bladder measured 10 × 3 cm and contained several mixed calculi. The wall measured 0.3 cm in thickness and the serosal surface had a ropy, nodular appearance. The mucosa appeared to be within normal limits. Microscopically, the gall bladder mucosa was intact and lined by normal columnar epithelium (fig 1). The wall deep to the muscle layer and subserosa contained large prominent nerve trunks, some of which were dumbbell-shaped, simulating a plexiform neurofibroma (fig 1). The enlarged nerves were accompanied by an increase in the number of ganglion cells embedded within proliferating Schwann cells (ganglioneuromatosis) (fig 2). Occasional "giant ganglia" were also seen. These foci were scattered randomly throughout the gall bladder wall. A mild chronic inflammatory infiltrate with attendant fibrosis was also present. The slides from the first thyroid tumour were reviewed and these, together with the

Figure 2 Associated with the neuronal hyperplasia were areas of ganglioneuromatosis with ganglion cells and proliferating Schwann cells (haematoxylin and eosin).

current tumour, were typical of medullary carcinomas. Associated areas of C-cell hyperplasia were present. Both adrenal tumours were classic solitary pheochromocytomas.

The Schwann cells and nerve trunks were strongly positive for S-100 protein and neurofilament. The ganglion cells were focally positive for neurofilament but negative for all other markers.

Discussion

Ganglioneuromatosis is a consistent finding in MEN 2b.⁵ In fact, one of the most characteristic and evident alimentary tract manifestations of the syndrome is diffuse or nodular enlargement of the lips caused by ganglioneuromatosis.^{6,7} Major reviews of the gastrointestinal pathology encountered in MEN 2b, however, have only briefly alluded to gall bladder disease.^{4,6}

In his initial review Carney found two patients with gall bladder disease.⁴ One had gall bladder ganglioneuromatosis and the other acalculous cholecystitis. Unfortunately, microscopical examination findings were not available in the latter case. Symptoms related to gall bladder disease are not a common or well documented mode of presentation in MEN 2b.

Ganglioneuromatosis of the gastrointestinal tract causes a plethora of abdominal symptoms, including constipation, diarrhoea, colic, projectile vomiting, and, in the case of infants, difficulty with feeding. Despite these protean manifestations, the usual gastrointestinal symptoms in MEN 2b are intermittent, chronic constipation and chronic diarrhoea.⁶ Ganglioneuromatosis is a well

recognised cause of gastrointestinal hypomotility and the associated diarrhoea has been ascribed to high circulating serum calcitonin concentrations produced by medullary carcinoma of the thyroid.⁶ Other peptides, however, may also play a part.

In this case the ganglioneuromatosis of the gall bladder wall might have resulted in poor contraction with a resultant stasis contributing to the formation of the gall stones. It must be remembered, however, that cholelithiasis is common and may be unrelated to the presence of ganglioneuromatosis of the gall bladder.

This case illustrates a very uncommon presentation of a patient with classic MEN 2b who had cholelithiasis and cholecystitis with synchronous, asymptomatic recurrent medullary thyroid carcinoma and bilateral adrenal pheochromocytomas.

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