bone marrow was made; these tumours have been shown to produce PTH-rP.[4-6]

Discussion

Raised serum calcium leads to increasing urinary calcium excretion; whether the urinary calcium excretion is appropriate for a given serum calcium can be determined from previously described nomograms (fig 1).[3]

A two hour timed urine collection and a blood sample during the middle of the urine collection are obtained after a 12 hour overnight fast for the measurements of calcium, phosphate, and creatinine. Calcium excretion is expressed as urine calcium multiplied by plasma creatinine, the product divided by urine creatinine. The calcium excretion and serum calcium in our patient were plotted and resulted in the point marked A on fig 1. The extrapolation of this point to intersect the curvilinear line at B represents the tubular reabsorption. The tubular component was estimated to be 3.05 mmol/l using this scheme in our patient. To correct for calcium retention because of renal failure, calcium excretion was recalculated using a value for plasma creatinine of 0.1 mmol/l (mean value of the reference range). Replotting calcium excretion against plasma calcium and extrapolating to the curvilinear line results in point C, the difference between B and C being the component due to reduced GFR. These investigations also showed an inappropriately high phosphate excretion for the concentration of serum phosphate.

PTH, 25O-HD, and 1,25-OHD can all cause increased tubular reabsorption of calcium, although only PTH can produce relative phosphaturia. As PTH was low, the relatively increased phosphate and reduced calcium excretion in urine in our patient was suggestive of the presence of another molecule with PTH-like activity. The finding of increased PTH-like activity in the presence of a suppressed plasma immunoreactive PTH indicated the possibility of a malignant tumour producing PTH-rP, and allowed us to intensify the search for a malignancy. This was confirmed by the documentation of raised immunoreactive PTH-rP. The use of this simple diagnostic test proved extremely helpful in the management of this patient with occult lymphoma. The clinical usefulness of the calcium and phosphate nomograms has diminished since the availability of reliable and speedy PTH assays. However, this case proves the value of simple and readily available laboratory measurements demonstrating PTH-like activity, which can aid the appropriate investigation and management of calcium disorders, and deserves to be more widely used in cases of obscure hypercalcaemia.

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Neuroendocrine cell hyperplasia in colonic tissue used for long term augmentation cystoplasty

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Abstract

A case is described of neuroendocrine cell hyperplasia in intravesical colonic mucosa, implanted previously during augmentation cystoplasty. The patient was a 28 year old man born with posterior urethral valves, a non-functioning right kidney, and a poorly functioning dilated left kidney. The hyperplasia consisted of pure neuroendocrine acini and tubules within the lamina propria, separate from the normal intestinal glands. Adjacent intraepithelial colonic neuroendocrine cells were increased diffusely. Rectal biopsy and previous biopsies of intravesical colonic tissue contained normal neuroendocrine cell populations. Implantation of gut segments into the urinary tract predisposes to late neoplasia, but there is only one report of carcinoid tumour in uroenteric tissue. Intestinal neuroendocrine cell hyperplasia usually occurs diffusely rather than as aggregates, except when associated with adjacent carcinoid tumour. Both diffuse and nodular hyperplasia were present in this case, with an unusual and striking morphology. This is the first report of neuroendocrine cell hyperplasia in gastrointestinal tissue implanted into the urinary tract; this raises the possibility of a risk of late carcinoid tumour in uroenteric segments.
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Keywords: bladder augmentation; neuroendocrine cell hyperplasia

In urinary tract reconstruction, gastrointestinal segments are used to create urinary conduits and for partial or complete bladder replacement, including augmentation cystoplasty. These procedures may give rise to complications such as metabolic imbalance, infection, urolithiasis, and neoplasia.[1 2] The oldest of these procedures is ureterosigmoidostomy. Its association with late neoplasia is well established, with a high risk of colonic adenocarcinoma at the anastomosis. When intestinal mucosa is exposed to both faecal stream and urine, faecal bacteria may produce carcinogens, particularly nitrosamines, from urinary contents. Mechanical trauma, suture material, chronic inflammation, and the abnormal interaction of different mucosae at the anastomosis may also be important.[1 2] It has been recognised recently that bowel implants, including bladder augmentations, that are exposed to urine without faeces also have an increased risk of malignancy; this has been estimated at 2% after more than 10 years.[2 3] The tumour types (predominantly adenocarcinoma and transitional cell carcinoma), site, and latent periods are similar in both circumstances.

Gut neuroendocrine cell proliferations comprise neoplasms, including carcinoid tumours and neuroendocrine carcinomas, and hyperplasias.[4 5] Hyperplasias of antral gastrin producing cells (G cells) or of enterochromaffin-like (ECL) cells in oxyntic (acid producing) mucosa, have long been recognised in the stomach. G cell hyperplasia may be primary or secondary, particularly in low acid states, whereas ECL cell hyperplasia is caused by hypergastrinaemia. In both, increased numbers of neuroendocrine cells are present either in their normal intraepithelial position in gastric glands or as aggregates in the lamina propria.[4]

Diffuse hyperplasia of mucosal intraepithelial enterochromaffin cells occurs in the small intestine in untreated coeliac disease, and in the colon in chronic inflammatory bowel disease.[5] Neuroendocrine cell hyperplasia in the form of nodules in the lamina propria may occur beside large and small intestinal carcinoid tumours,[5] but to our knowledge, this has only once been reported without co-existing malignancy, in a case of megacolon.[6]

We present a case of combined nodular and diffuse neuroendocrine cell hyperplasia, without concurrent carcinoid tumour, in colonic mucosa used for augmentation cystoplasty. We know of no previous reports of neuroendocrine hyperplasia in uroenteric implants.

Case report

This 28 year old man was born with posterior urethral valves, a non-functioning right kidney, and a poorly functioning dilated left kidney. In infancy he had a right nephrectomy and left cutaneous ureterostomy. The left ureter was later implanted into his bladder but, because of upper urinary tract deterioration, ileal loop urinary diversion was performed in childhood. He then suffered intermittent stomal obstruction with worsening renal function.

At 18 years old the urinary diversion was reversed; at operation the ileal conduit was grossly dilated with significant renal distension. To avoid a second failed ureteric implantation, the bladder was augmented using a sigmoid colon segment and the ureter re-implanted into the latter. Four years later, reduction cystoplasty, removing part of the colonic tissue, was performed because of poor bladder emptying. In addition, there were multiple ureteric re-implantations because of stenoses.

Eventual dialysis was followed after four years by a renal transplant. His renal function was then normal and stable with good bladder function. Two months after the transplant, several episodes of urinary tract infection necessitated a left native nephroureterectomy, which is the subject of this report.

Pathological findings

The specimen comprised a severely hydronephrotic kidney, measuring 130 × 60 × 30 mm, with a 90 mm length of dilated ureter. Microscopy of the kidney showed end stage disease. The unexpected finding was in a fragment of large intestinal tissue, which had previously been used for augmentation cystoplasty, attached to the distal ureter.

The colonic mucosa showed an unusual form of neuroendocrine hyperplasia, composed of individual clusters, acini, and tubular glands within the lamina propria (fig 1). These aggregates contained a pure neuroendocrine cell population, without enterocytes or goblet cells. This was clearly demonstrated by Masson Fontana/periodic acid Schiff (PAS) (fig 2A) and diazo staining (that is, both argyrophil and argentaffin), and by immunohistochemistry with an antibody against chrom-

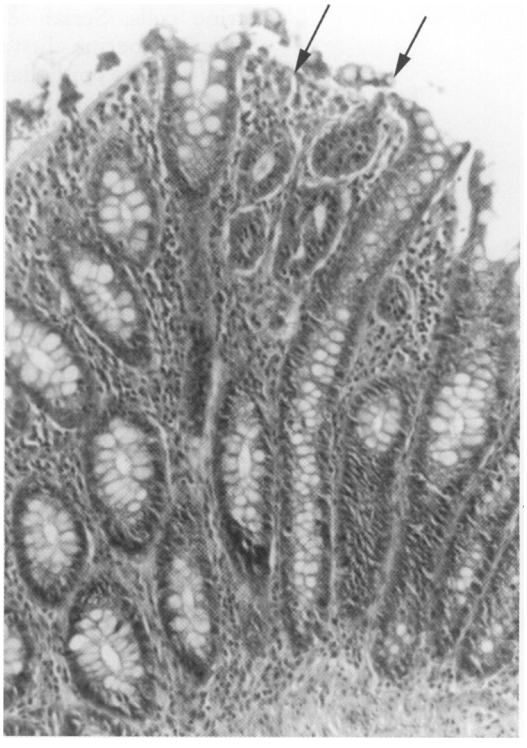

Figure 1 Colonic mucosa with neuroendocrine cell hyperplasia in the form of individual acini and glands in lamina propria (arrows) (haematoxylin and eosin).

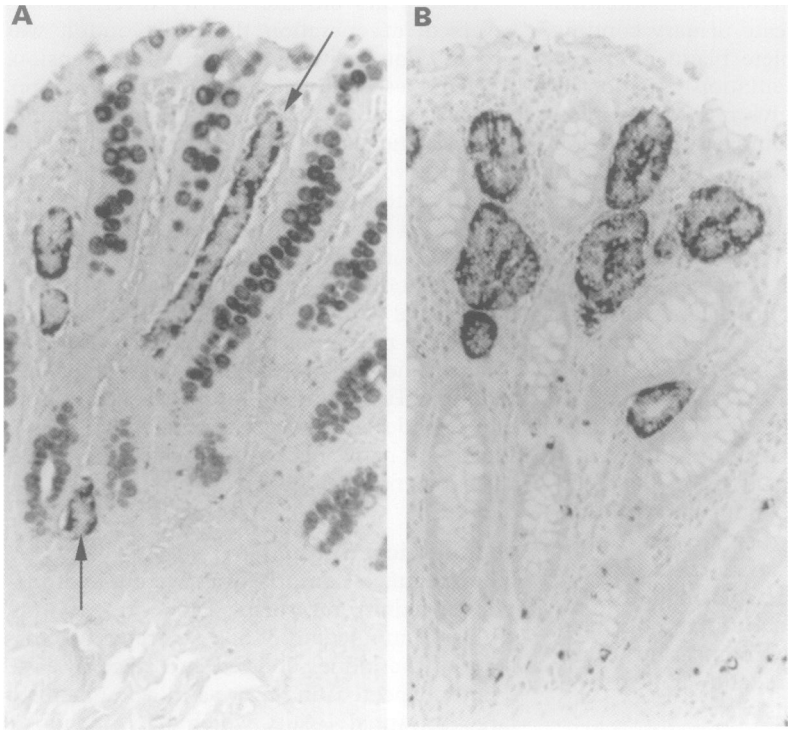

Figure 2 (A) Colonic mucosa with neuroendocrine cell hyperplasia (arrows) (Masson/PAS). Neuroendocrine tubule extends to luminal surface: serial sections do not show communication with colonic epithelial glands. (B) Colonic mucosa with neuroendocrine cell hyperplasia (chromogranin). Intraepithelial neuroendocrine cells are also diffusely increased.

ogranin A (Dako Ltd, High Wycombe, Bucks, UK) (fig 2B). Additional immunohistochemistry showed strong positivity for neurone specific enolase, somatostatin, and serotonin, and weak positivity for gastrin, pancreatic polypeptide, and prostatic acid phosphatase. The neuroendocrine aggregates were distributed mainly superficially in the lamina propria, contrasting with the usual predominantly basal location of intraepithelial neuroendocrine cells. Serial sections showed that the neuroendocrine clusters did not communicate with colonic epithelial glands but that some of the neuroendocrine tubules opened onto the luminal surface and a few extended into the lower mucosa (fig 2A).

The colonic intraepithelial neuroendocrine cells were also diffusely increased in number, with occasional linear aggregates, but remained mostly basal. They did not extrude into lamina propria or communicate with the lamina propria neuroendocrine aggregates. The neuroendocrine hyperplasia was confined to the mucosa, without involvement of submucosa or of ureteric or renal tissue.

Rectal biopsy was normal and showed no increase in neuroendocrine cells. Intravesical colonic mucosal biopsies six years earlier showed only moderate chronic inflammation.

Discussion

We are not aware of previous reports of neuroendocrine hyperplasia in uroenteric implants. Previous histological studies of the mucosa of colonic conduits, exposed to urine only, showed progressively increasing chronic inflammation, without dysplasia, during long term follow up.[7] Augmentation cystoplasty in animals produced transitional metaplasia and hyperplasia at the anastomotic junction, together with occasional papillary tumours.[8] These studies did not specifically discuss the neuroendocrine cell population. There has been a single case report of a goblet cell adenocarcinoid tumour in a ureteroileal conduit[9]; the tumour was predominantly submucosal, and the mucosal neuroendocrine cells were not described.

In our case, the normal rectal neuroendocrine population suggests that the hyperplasia is unlikely to have been a generalised large bowel abnormality. The previous normal biopsies of intravesical colonic tissue indicate that the hyperplasia was either focal or had recently developed. Gut neuroendocrine cell density appears to be related to the requirement for coordination of mechanical and secretory activities.[4] The previous case of colonic nodular neuroendocrine hyperplasia with formation of acini occurred in a megacolon.[6] Our patient suffered poor bladder emptying, requiring bladder reduction, and ureteric stenoses. Obstruction and dilatation are features of both cases; neuroendocrine hyperplasia may therefore represent a response to mechanical dysfunction. It has also been postulated that chronic inflammation may cause gut neuroendocrine hyperplasia,[5] but as most chronic inflammatory gastrointestinal diseases are also associated with altered motility, the precise pathogenesis of neuroendocrine hyperplasia remains unclear.

The diffuse and nodular pattern of intravesical colonic neuroendocrine cell hyperplasia seen here is similar to that occurring adjacent to intestinal carcinoids.[5] The latter may be associated with diffuse intraepithelial neuroendocrine cell hyperplasia, with intraepithelial aggregates and neuroendocrine buds into the lamina propria[5]; such budding was not identified in our case. Diffuse and nodular neuroendocrine hyperplasia also occurs in gastric G cell and ECL cell hyperplasias.[4] It is known that patients with chronic renal failure often develop hypergastrinaemia.[10] Most gastric ECL cell carcinoids are gastrin dependent,[4 5] while intestinal carcinoid tumours are considered not to be gastrin dependent. Nevertheless, it is possible that increased gastrin could have contributed to the colonic neuroendocrine hyperplasia, perhaps superimposed on altered motility and chronic inflammation.

While our case resembles these other forms of gut neuroendocrine hyperplasia, its morphology, with well defined intramucosal neuroendocrine acini and tubules connected to the luminal surface, is striking and highly unusual. Together with the previous report of a goblet cell adenocarcinoid tumour in a ureteroileal conduit,[9] this case raises the possibility of a risk of late development of carcinoid tumour in uroenteric implants.

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