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Xanthomatosis of the gastrointestinal tract with focus on small bowel involvement

Accumulation of foamy lipid-laden histiocytic cells is most often seen in the skin and tendons, usually associated with congenital or acquired hyperlipidaemia, as seen in patients with diabetes mellitus, obstructive jaundice, and familial hypercholesterolaemia. The pathogenesis of xanthomatous lesions in other sites, including the urinary bladder,¹ prostate,² and gastrointestinal tract seems to be less consistent. Within the gastrointestinal tract the gastric mucosa is the most frequently cited location. Involvement of the oesophagus and bowel has rarely been described. Only three such cases largely confined to the small bowel have previously been documented. We here present an additional small bowel example accompanied by a short review of the existing literature in English on gastrointestinal xanthomatous lesions, including a discussion on its possible pathogenesis.

Histologically, the lesion is unique and a correct diagnosis does not pose significant difficulties. Identification of diverse phagocytosed cytoplasmic deposits in other histiocytic lesions may require ancillary studies. More importantly, malignant lesions composed of clear cells or signet ring cells, primary or metastatic,^{3–4} need consideration. With a high index of suspicion coupled with appropriate histochemical and immunohistochemical reactions, the correct diagnosis will easily be accomplished. The process is characterised by aggregates of foamy histiocytes, unaccompanied by fibrosis or giant cells as seen in xanthogranulomatous lesions.⁵ Well-defined clusters of such foamy histiocytes have been labelled xanthoma.^{6–8} The diffusely infiltrating counterpart has been termed xanthomatosis.^{9–10} When forming a bulky mass lesion, the label xanthomatous pseudotumour has been applied^{11–12} and the subtle collection of xanthoma cells is often referred to as xanthelasma.¹³ In this letter we collectively refer to these lesions, which may be related, as xanthomatous lesions (XAN).

Case report

A woman in her 70s with a CT-verified ruptured infrarenal abdominal aortic aneurysm was admitted for surgery. Her past medical

history included only arterial hypertension. During the operation the surgeon noticed a pale sigmoid colon but found no indication for a sigmoid resection.

On day 1 after her initial operation she developed a metabolic acidosis; sigmoidoscopy showed changes suggestive of necrosis. A subsequent explorative laparoscopy confirmed these findings and a sigmoid resection was performed. The small intestine and the remaining colon were peroperatively described as vital.

During her subsequent stay in the intensive care unit (ICU) she had recurrent hypotensive episodes and several incidents of metabolic acidosis. She also underwent haemodialysis for acute renal failure and developed critical illness polyneuropathy (CIP).

Seventeen days after the sigmoid resection, fresh bleeding was noted from the colonostomy, interpreted as ischaemic changes in the caecum. Consequently, a third laparotomy was performed, with resection of the remaining colon with a rim of the terminal ileum as well as an additional segment of the small bowel, which focally appeared pale and was wrapped in fibrous bands. Five months after the initial admission she was discharged from the ICU. She died shortly thereafter from respiratory failure as a result of CIP. Permission for autopsy was granted.

Pathology

The surgical specimens submitted encompassed the resected sigmoid colon arising from the second laparotomy, the remaining colon with adjacent terminal ileum and the resected ileum from the third laparotomy. The material obtained was processed in accordance with routine techniques, and stained with H&E, PAS (periodic acid Schiff) with and without diastase, alcian blue at pH 2.6, Ziehl–Neelsen stain and von Kossa stain as well as immunohistochemically for the histiocytic marker CD68 and the epithelial markers CK, KI 1 and CAM 5.2.

Grossly the sigmoid colon measured 30 cm in length. The central 17 cm had a dark discoloured mucosa. No polyps or tumours were noted. The remaining colon with the terminal ileum (from the third laparotomy) showed intact mucosal folds with no areas of dark discoloration or ulceration. The wall was focally thickened. On the serosal aspect dark discoloration of the surrounding fat and omentum was noted. The separately submitted ileum measured 60 cm in length; the mucosal texture appeared normal apart from a 15 cm segment showing reduced height of the mucosal folds and ulcerations. The wall was thickened and had a yellowish hue. Macroscopically, the tissue looked viable.

Histological examination of the specimen from the second laparotomy featured necrosis of the mucosal layer and focal necrosis of the submucosa and luminal part of the muscularis propria. Transmural necrosis was not seen. There were no signs of XAN in the sigmoid colon.

Histological examination of the specimens from the third laparotomy disclosed extensive ulceration of the small bowel mucosa corresponding to the grossly abnormal zone. The intestinal wall was markedly thickened due to diffuse infiltration with xanthomatous cells permeating all layers of all parts of the specimen examined, including areas devoid of ulceration (figs 1 and 2).

Cytologically, the macrophages had distinct cell membranes, abundant eosinophilic granulated and vacuolated cytoplasm, and medium-sized centrally placed nuclei with dense chromatin. Mucin staining was negative. The lesional cells were immunonegative for CK, KI 1 and CAM 5.2, but positive for CD68 (fig 2), consistent with their histiocytic nature. The caecum showed sparse infiltration with cells of a similar morphology. The lesion was not accompanied by fibrosis and giant cells were not apparent. There were no Michaelis–Gutmann bodies, nor any viral inclusion bodies, acid-fast bacteria or fungi.

The autopsy showed no further macroscopic lesions. Microscopic examination of the remaining small intestine likewise showed no additional areas of XAN.

Discussion

The vast majority of XAN are tiny lesions, solitary or multiple, occasionally involving several compartments of the gastrointestinal tract, such as the rectum and duodenum,¹⁴ and oesophagus and stomach.¹⁵ Sizeable XAN, producing a mass and/or bleeding, as in the current case, are infrequent. Such lesions may involve a major portion of one gastrointestinal segment and additionally permeate adjacent organs, such as the gastric example with involvement of the oesophageal submucosa, duodenal subserosa and peripancreatic fat, reported by Fernández-Alonso *et al.*¹² Small bowel XAN with microscopic permeation of the adjacent caecum, as seen here, was also noted by Goodman.¹⁰

According to the literature, gastrointestinal XAN most commonly involves the stomach but with significant variations in the reported incidence. A Japanese autopsy study disclosed

Figure 1 Small bowel permeated by xanthomatous cells, involving the mucosa (H&E).

Figure 2 Abundant xanthomatous cells in the muscularis propria (H&E), displaying immunopositivity for CD68 (inset).

XAN in 58% of patients.¹⁶ Among 900 gastric biopsies, Pieterse reported seven examples of gastric XAN.⁷

A recent paper suggests that rectal involvement may be more prevalent than the sparse literature suggests. Thus papules of XAN were seen in 2 of 100 consecutive rectal biopsies.¹³ XAN is, on the other hand, distinctly unusual in the oesophagus and small bowel as reported here.

We are aware of only one report in the English language literature of XAN confined to the oesophagus, which concerned an incidentally found 5 mm large lesion, described as a verruciform XAN.¹⁷ Another report, which is only available as an abstract,¹⁵ presented a single case, which in addition to oesophageal XAN, also featured XAN in the stomach.

The gastric XAN is generally less than 5 mm, single or multiple, and is located in the mucosa and submucosa.^{7 16 18 19} Most authors have failed to document any relationship to hyperlipidaemia.^{7 18–20} Gastric XAN is generally an incidental finding of minute dimension in biopsy specimens. One case of a large gastric XAN, described as a pseudotumour, was documented incidentally in an autopsy of an HIV-positive 48-year-old male.¹²

Small intestinal XAN is an unusual condition. Apart from the submucosal XAN in the efferent jejunal loop of a Billroth II type operation, which coexisted with XAN in the gastric remnant, reported by Mast *et al.*,²¹ only three small bowel examples have previously been documented. Whereas the present case displayed transmural involvement, none of the previously reported cases featured xanthomatous cells in the mucosa. Coletta and Sturgill⁹ reported the case of a 54-year-old man with disseminated hepato-cholangiocarcinoma and a prior history of alcohol abuse and infectious hepatitis. Serum lipids were normal. He was treated with chemotherapy and radiotherapy to the left hemipelvis. Prior to death, he developed wine-coloured stools, and decreased motility and dilatation of the small bowel was demonstrated. Radiological aspects of this case have been published elsewhere.²² Autopsy findings encompassed isolated XAN involving an 85 cm long jejunal segment, which histologically featured a xanthomatous infiltrate affecting the submucosa, muscularis propria and serosa. Goodman¹⁰ reported a case of a 33-year-old man with AIDS who underwent a right hemicolectomy because of abdominal pain and ileal stenosis of unknown cause. Three months prior to admission he was treated for cytomegalovirus colitis. Serum lipids were normal. Microscopic examination of the terminal ileum and the adjacent caecum showed a diffuse xanthomatous infiltrate affecting the muscularis propria.

Small bowel XAN was diagnosed in a 9-year-old boy who presented with abdominal pain and obstruction of the proximal small bowel one month after chemotherapy for Burkitt's lymphoma.¹¹ The resected small bowel was devoid of neoplastic disease but comprised an annular constricting XAN in the submucosa, muscularis propria and serosa.

Colonic XAN is occasionally associated with abnormalities of lipid metabolism. Nakasono *et al.*²³ reported hyperlipidaemia in 7 of 25 patients with colorectal XAN. Gaster *et al.*²⁴ presented a female patient who was hypercholesterolaemic for many years. Radiological evidence of small bowel involvement was also provided; however, only the large bowel XAN was verified histologically. Three other patients with colonic

XAN and increased serum lipids have been reported.^{8 25 26} Most cases of large bowel XAN are, however, unassociated with increased serum lipids. Coexistence of multiple myeloma and extensive XAN in the form of multiple papules, including rectal involvement has been reported.¹⁴

No single event accounting for XAN has been identified. In the gastric cases intestinal metaplasia and chronic inflammation have been considered of significance; 6 of 7 cases reported by Pieterse⁷ displayed such features. Similar observations were made by Moretó *et al.*¹⁹ An altered absorptive activity of intestinal metaplastic epithelium has been considered a possible mechanism.⁷ Considering the high prevalence of chronic gastritis and intestinal metaplasia in gastric biopsies, one may argue that this coexistence is purely coincidental. However, XAN rarely, if ever appears in the normal gastric mucosa. Previous gastric surgery and bile reflux may likewise predispose to XAN.^{18 27} Miliauskas⁶ put forward the theory that xanthomatous lesions are most likely to be the result of previous quiescent damage, for example local trauma or subclinical infections. Along the same line is the observation of histiocytic cells in rectal biopsies showing signs of active epithelial damage, indicative of these cells being part of a reparative process.¹³

Goodman¹⁰ argues that the resulting XAN may have been initiated by cytomegalovirus colitis acting as a predisposing insult. The possibility of an iatrogenic lesion, elicited by chemotherapy of lymphoma/therapy of cytomegalovirus colitis should, however, also be considered. Thus, a temporal relation between chemotherapy of the small bowel lymphoma¹¹ and the development of XAN was noted. A comparable example of gastric XAN diagnosed after chemotherapy of lymphoma is also available.¹² The significance of radiotherapy in the development of XAN has been discussed. In a recent publication on oesophageal verruciform xanthoma, developing in a patient previously receiving thoracic radiotherapy to treat lymphoma, an aetiological role of radiation was considered likely.¹⁷ However, Coletta and Sturgill⁹ disregard radiation as a triggering factor, emphasising the notion that XAN is not a well recognised sequel to irradiation. The occasional aggregate of foamy cells in the intima of arteries in radiated tissue²⁸ is not considered part of XAN. Furthermore, the well established radiation-induced changes of bowel wall, such as mucosal atrophy, submucosal fibrosis and obliterative endarteritis²⁸ were not described or illustrated in their case. It is noteworthy that one of the cases of small bowel XAN concerned an AIDS patient since it is well established that immunocompromised subjects more readily develop xanthomatous responses.²⁹ It is not inconceivable that the other cases of small bowel XAN were immunodeficient as well. Whether the currently presented patient was immunocompromised is unclear. Nor was her serum lipid status determined. Although none of the previously reported cases of small bowel XAN were associated with hyperlipidaemia, our patient may have had increased serum lipids, considering her severe arteriosclerotic disease. She had several episodes of intestinal ischaemia documented histologically as well as ileal transmural XAN. It is likely that the ischaemia played a role in the development of the XAN, which may be the end result of reparative processes following successive periods of hypoperfusion. Such coexistence of intestinal

ischaemia and XAN has, however, not previously been reported. Hence, some additional unknown event may have triggered the massive accumulation of foamy histiocytes. The proposed functional relationship between ischaemic damage of epithelial cells and the accumulation of signet ring cells^{30–32} is, however, noteworthy. Whereas a spectrum of cellular and membranous degenerative changes probably constitutes the initiating event, the circumstances required for the formation of the full blown gastrointestinal XAN may be diverse and are often not well established. Ultrastructural studies have shed some light on the origin and/or evolution of XAN in some other clinical settings.^{33–36} Subcellular observations on XAN of the alimentary canal are, however, sparse,^{10 13 14} describing the cytoplasmic accumulation of lipid droplets and lysosomes as well as disrupted membranes in histiocytic cells.

In this letter, we have considered xanthomatous lesions of the gastrointestinal tract collectively, presuming that such lesions are related, irrespective of their size and sublocation in the gastrointestinal tract. The correlation between the dimensions of the single XAN lesion and its location is, however, noteworthy. Thus, apart from the coexistent, probably secondary microscopic involvement of the caecum by ileal XAN, as reported here and by Goodman,¹⁰ large bowel XAN is usually confined to the recto-sigmoid portion and features tiny papules, solitary or multiple, usually measuring less than 6 mm,^{6 23 26} as judged from the sparse literature. Similar morphology characterises most gastric examples. The background morphology of the latter is, however, usually altered, as opposed to the generally normal background morphology of colorectal XAN. As opposed to the modest dimensions of most gastric and colorectal XAN, all four documented cases of small bowel XAN were large and produced symptoms that led to abdominal exploration. This discrepancy may at least in part be ascribed to the fact that the gastric and recto-sigmoid mucosa is much more frequently biopsied, whereas the small bowel lesion may remain undiagnosed until a large size is reached.

In summary, several mechanisms may lead to xanthomatous lesions of the gastrointestinal tract. It is most likely that XAN *per se* is the result of an unusual reaction to various insults, iatrogenic or spontaneous, in predisposed individuals, rather than representing a specific lesion. Whether the tiny XAN developing in gastric and rectosigmoid colon differ pathogenetically from the sizeable small bowel cases is presently unclear.

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Pure cartilaginous teratoma of the testis: an immunohistochemistry and fluorescence in situ hybridisation study

In the testis pure teratomas are rare, accounting for less than 7% of primary testicular tumours.¹ This contrasts with the ovary, where 95% of germ cell tumours are pure teratomas.² Teratomas do not always contain tissues representing all three germ cell layers. A monodermal teratoma is one that consists of only one germ cell layer, endoderm, mesoderm or ectoderm. The best recognised monodermal testicular teratomas are carcinoid tumours and primitive neuroectodermal tumours.³ Monodermal teratoma composed solely of cartilage is rare. We report a second case of purely cartilaginous teratoma and provide interphase cytogenetic evidence of its germ cell origin.

Case report

A 21-year-old man presented with a mass in his right testis. Blood chemistry tests showed an increased level of β -hCG (641 IU/l; normal range 0–3 IU/l), and a normal level of α -fetoprotein (2.4 ng/l; normal range 0.0–8.0 ng/l). The patient underwent orchiectomy followed by chemotherapy. Three months later, retroperitoneal lymph node dissection was done, removing a 275 g paracaval and inter-aortocaval mass, periaortic lymph nodes, and pericaval mass.

Methods

Immunohistochemistry

Sections 4 μ m thick were cut from the paraffin block and stained with H&E. Immunohistochemistry for OCT4 was accomplished with a polyclonal goat anti-OCT4 antibody (C20, sc 8629; Santa Cruz Biotechnology,

Santa Cruz, CA, USA; 1:500 dilution, 30 min at room temperature) directed towards the –COOH terminus of the protein, as previously described.^{4,5} Antigen retrieval was carried out by heating sections in 1 mmol/l EDTA (pH 8.0). Endogenous peroxidase activity was inactivated by incubation in 3% H₂O₂. Non-specific binding sites were blocked using Protein Block (DAKO Corp., Carpinteria, CA, USA). Immunohistochemistry for S100 protein was also performed (primary antibody 1:1000 dilution; 30 min incubation; DAKO). Antigen retrieval was performed by heating sections in pH 6.0 citrate buffer. The positive and negative controls performed appropriately for each procedure.

Fluorescence in situ hybridisation

Fluorescence in situ hybridisation (FISH) was performed on the testicular tumour as previously described.⁶ Sections (4 μ m) were prepared from buffered formalin fixed, paraffin embedded tissue block. The slides were deparaffinised prior to hybridisation. Dual-colour FISH was performed by using a mixture of Spectrum Orange labelled centromeric α satellite DNA probe (CEP12 located at 12p11.1–q11, locus D12Z3) and Spectrum Green labelled subtelomeric DNA probes (Tel12 located at D12S2071) for chromosome 12p (probes from Vysis, Downers Grove, IL, USA).

The slides were examined using a Zeiss Axioplan 2 microscope (Zeiss, Göttingen, Germany) with these filters: SP-100 DAPI, FITC MF-101 for Spectrum Green (12p) and Gold 31003 for Spectrum Orange (CEP12) from Chroma (Chroma, Brattleboro, VT, USA). The images were acquired with a CCD camera and analysed with MetaSystem Isis software (MetaSystem, Belmont, MA, USA). Five sequential focus stacks with 0.4 μ m interval were acquired and then integrated into a single image in order to reduce thickness-related artefacts. The images were adjusted to reduce background through threshold adjustment; however, the relative signal intensity and signal locations were not changed.

From the tumour section, 100 nuclei were scored for signals from CEP12 (red) and 12p (green) under the fluorescence microscope with 1000 $\times$ magnification, and the ratio between green and red signals was subsequently calculated. We analysed the spatial distribution of the green and red signals to detect the specific patterns of signal aggregation consistent with isochromosome 12p (i(12p)), as previously reported.^{1–11} The quantitative criteria to determine 12p overrepresentation were described previously.^{6–10–12} A classical seminoma specimen was used as a positive control for FISH analyses.

Results

Pathological findings

The cut surface of the testis revealed a 20 $\times$ 14 $\times$ 10 mm well-circumscribed, white, lobulated rubbery mass located within the testicular parenchyma. Histological examination revealed the mass to be composed of mature cartilage (fig 1). The remaining testicular parenchyma showed seminiferous tubules containing only Sertoli cells. No intratubular germ cell neoplasia, unclassified type (IGCNU) was visible. A focus of fibrous scar was present outside the cartilaginous tumour suggestive of a burnt-out germ cell tumour.

The retroperitoneal lymph node dissection specimens showed necrosis and inflammation