normal CT brain scan. Laboratory examination of the CSF showed 270 white blood cells/mm³ (66% lymphocytes, 34% neutrophils) with a protein level of 0.79 g/l. In view of the clinical presentation and CSF findings, treatment was aimed at a presumptive diagnosis of meningoencephalitis with a combination of ceftriaxone and aciclovir. Serum and CSF samples were sent for herpes simplex virus (HSV) and Epstein-Barr virus (EBV) titres and PCR, which were later reported as negative.

On transfer to the intensive care unit he was electively intubated and ventilated. Treatment with intravenous piperacillin-tazobactam and ionotropes was commenced. Elective surgical tracheostomy was performed on day 8 and sedation ceased to allow for regular neurological examination. By day 11 there had been no neurological improvement, with no response to deep pain stimuli and hypotonia. The Glasgow Coma Score was estimated to be 7/15 at this point. An MRI scan of the brain revealed an ill-defined T₂ hyperintense area in the brainstem which was reported as an area of infarction secondary to cerebrovascular ischaemia. An MRI scan of the spine also showed mild degenerative changes. An EEG was performed which excluded non-convulsive status epilepticus.

On day 13 he was noted to be more responsive to stimuli but remained quadriplegic. By day 15 he was alert, obeyed commands, and had begun to recover some upper limb control. By day 18 his upper limbs continued to improve although his lower limbs remained paralysed. Electromyography on day 22 revealed mild subacute axonal loss, no evidence of demyelination and absent F-waves. On day 30 he was weaned off positive pressure ventilation.

The laboratory reported a high titre of *C jejuni* IgM on day 37. Because detection of the IgM antibody response to *C jejuni* could be unreliable,⁵ we confirmed the diagnosis of *C jejuni* infection by demonstrating a significant rise and subsequent fall in the titres of IgM, IgG and IgA antibodies (table 1). After careful consideration, a 5-day course of immunoglobulin was commenced to treat possible BBE. Before starting this treatment, serum for anti GQ1b antibodies was sent to the laboratory which was later found to be negative. Although many features of this case fit into the classical description of BBE, there were a number of atypical findings such as a CSF pleocytosis and a negative anti GQ1b. Other conditions mimicking the presentation of BBE such as multiple sclerosis, acute disseminated encephalomyelitis, brainstem tumour, myasthenia gravis, botulism, Wernicke's encephalopathy and vasculitis were excluded. On day 52 the patient was transferred to the local brain injury unit where he continued to display neurological recovery with intensive rehabilitation. The patient has now regained most of his neurological function.

Discussion

BBE is a rare complication of *Campylobacter* food poisoning⁷ resulting in an ascending polyneuropathy.⁸ It may be related to certain genetic polymorphisms in the host which can be correlated with the severity of the disease. A high incidence of autoantibodies against glycoconjugates such as GM₂, GD1a and GD1b is found among these patients.⁹ Similar epitopes have been shown to occur in the lipopolysaccharide antigens of *C jejuni* which

Take-home messages

- Bickerstaff's brainstem encephalitis is a rare but potentially life threatening complication of *Campylobacter jejuni* gastroenteritis.
- A high index of clinical suspicion and a close liaison with laboratory staff can facilitate an early diagnosis.
- For confirmation of the diagnosis it is essential to test sequential serum samples to demonstrate a significant rise and subsequent decline of IgM, IgG and IgA antibodies to *C jejuni*.

may represent the immunogenic stimulus. In addition, there is cross-reactivity between antigens from *C jejuni* and the P2 protein of the myelin sheath which may explain the pathogenetic connection between *C jejuni* infection and brainstem encephalitis.⁸

The lymphocytic pleocytosis and raised protein level in the CSF led us to start empirical treatment for both bacterial and viral meningitis. However, the acute onset of ophthalmoplegia, generalised limb weakness and reduced level of consciousness suggested BBE (table 2). *Campylobacter* was considered as an aetiological agent after a detailed history revealed that the patient had suffered an episode of diarrhoea a week before becoming acutely unwell. Subsequent serological examination confirmed the diagnosis of *C jejuni* infection. Although *C jejuni* infection can lead to a wide spectrum of neurological complications, this case did not display features consistent with a classical presentation of Miller Fisher syndrome or Guillain-Barré syndrome.

Further investigations of these patients include neuroimaging and electrophysiological studies. High-intensity areas on T₂-weighted images of the brainstem, thalamus, cerebellum and cerebrum on MRI are present in approximately one-third of patients, and these lesions can be erroneously reported as infarcts.⁷ EEG studies may show slow wave activity in the θ to δ range. Electromyography may reveal decreased motor nerve conduction studies, prolonged distal latency, reduced compound muscle action potential and absent or prolonged F-waves. As in this case, these findings are highly suggestive of axonal loss. Patients may have raised levels of anti-GQ1b IgG antibody, which is strongly associated with ophthalmoplegia.

Most patients can be managed by immunotherapy, using plasmapheresis or intravenous immunoglobulin either singly or in combination. Those patients who fulfil the diagnostic criteria of BBE usually have a good prognosis. Optimal effective treatment has not been established. Intravenous immunoglobulin has proved as effective as plasma exchange, while combined treatment with methylprednisolone and intravenous immunoglobulin is controversial.^{10 11}

BBE is a rare but important complication of *C jejuni* gastroenteritis. A high index of suspicion together with a detailed history and examination are essential in making an accurate diagnosis.

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Dermatofibrosarcoma protuberans in a patient with X-linked agammaglobulinaemia

This is the first case report of dermatofibrosarcoma protuberans (DFSP) arising in a patient with X-linked agammaglobulinaemia

(XLA). XLA is the prototypic genetic disorder resulting in a lack of antibody production. Mutations are found in the Btk gene, which results in arrest of B cell development from pro B cells to pre B cells and subsequently to mature B lymphocytes.¹ These patients are prone to recurrent infections without replacement immunoglobulin but are generally not at increased risk of malignancy. DFSP is a slow growing cutaneous tumour that has been reported previously with HIV infection and post-renal transplantation, but not with antibody deficiency.

Case report

A 46-year-old man, known to have XLA, presented in 2001 with a painless cystic subcutaneous swelling over the proximal interphalangeal joint of his right little finger. The swelling had gradually been increasing in size over the previous year. Plain radiographs of the area were normal. The lesion was excised and histology showed a subcutaneous nodule composed of densely packed spindle cells with tapering nuclei. Collagen was focally seen between the cells but there were no giant cells or foamy histiocytes, although mitoses were identified. The findings were those of a DFSP, which had been incompletely excised. Subsequent immunohistochemical staining demonstrated the tumour was CD34 positive and factor XIIa negative.

The lesion recurred 4 months later and was re-excised. However, histology, showed widespread recurrence and the finger was subsequently amputated with clear resection margins.

This man had originally been diagnosed with antibody deficiency at the age of 11 years and had been treated with intramuscular immunoglobulin injections initially. The diagnosis of XLA was made by demonstrating absence of the Bruton's tyrosine kinase (Btk) protein on Western blotting. Investigations showed absent circulating B cells with normal T cell numbers on flow cytometric analysis. Levels of serum immunoglobulin G, A and M were markedly reduced. Subsequent genetic analysis showed a four-base pair (TTTG) deletion between codons 1581 and 1584. This deletion results in a frameshift mutation leading to a stop codon, one codon downstream of the deletion, thus confirming the diagnosis of XLA. Prior to the diagnosis of DFSP, he had been diagnosed with bronchiectasis, presumed to be due to a delay in starting immunoglobulin replacement; however, this had been stable on replacement intravenous immunoglobulin treatment.

At present, 5 years after amputation of the affected finger, he continues to remain well with no recurrence of DFSP and there has been no evidence of metastases or other malignancy.

Discussion

DFSP is a rare monoclonal cutaneous soft tissue sarcoma accounting for approximately 1.8% of all soft tissue sarcomas in one series.² About 85–90% of DFSPs are low-grade lesions, although the remainder contain a high grade fibrosarcomatous component. It is an indolent tumour with a mean symptom duration of 6.4 years at presentation.³ Treatment of DFSP is wide local excision of the tumour, and the probability of controlling the tumour with this exceeds 90% although there is a less than 5% chance of distant metastases.² Radiotherapy has been used in the event of local disease that cannot be resected.

Patients with XLA typically suffer from recurrent sino-pulmonary infections with encapsulated bacteria. In addition, they are also prone to infections with giardia and enteroviruses.¹ The incidence of malignancy in patients with XLA is not clearly defined as no formal epidemiological studies have been performed. However, the frequencies reported in four large studies were 4 of 201, 0 of 73, 2 of 96 and 0 of 44.^{1–4–6} It should be noted that only the first two studies confirmed the diagnosis of XLA on a molecular basis. The other two studies were published prior to the description of Btk mutations in XLA and it has been suggested that some of the patients in these series might have had common variable immunodeficiency—a condition more frequently associated with malignancy.⁴ There have been case reports describing gastric adenocarcinoma,⁷ squamous cell carcinoma of the lung⁸ and lymphoreticular malignancy¹ in patients with XLA. In addition, the European Society for Immunodeficiencies (<http://www.esid.org>) XLA sub-registry was launched at the most recent biennial meeting in October 2006, and it will be interesting to see the data on the incidence of malignancy when it is available.

Conventionally, tumour immunity has been thought to be cell-mediated and DFSP has been described in the setting of immunodeficiency in two patients with the acquired immunodeficiency syndrome⁹ and three patients after renal transplantation,¹⁰ suggesting that T-cell-mediated immunity is likely to play a role in this tumour. However, although there might be a possible link with T cell immunocompromise, overall very few cases of DFSP have been reported in this setting.

The mutation in XLA, however, primarily affects antibody production. In the cases of patients with gastric and lung carcinomas, infection with *Helicobacter pylori* and chronic infection with bronchiectasis, respectively, were thought to play a role in the development of malignancy. It is also possible that in lymphoreticular malignancy, recurrent infection results in chronic stimulation of lymphocytes, accumulation of mutations and subsequent malignancy. Hence, the lack of antibody production is thought to increase the risk of chronic infections that can subsequently predispose to malignancy.

Btk is also expressed in non-lymphocytic cells and may have roles there. In addition to its role in B cell survival, there is data to suggest that Btk can mediate apoptosis as well.¹¹ DFSP is thought to arise from dermal fibroblasts but Btk is not known to be expressed in this cell lineage. Hence, it is unlikely that a Btk deficiency results in excess tumour survival in DFSP. However, Btk is also expressed in myeloid cells, including monocytes/macrophages and dendritic cells, and plays a role in the activation of these cells. It is important in NFκB activation and stimulation via toll-like receptors 2 and 4,^{12–13} although there is some conflicting data.¹⁴ Hence, there might be subtle defects in these antigen-presenting cells that might predispose towards a reduction in tumour immunity.

In our patient with XLA, there was no evidence of chronic cutaneous or soft tissue infection at the site of the tumour. Consequently, it is unclear why XLA should predispose to development of DFSP. The possibilities are that antibody or B cell (as antigen presenting cell) deficiency in some way contributes to tumour immunity, lack of Btk might result in subtle myeloid/antigen

Take-home messages

- This is the first published case of dermatofibrosarcoma protuberans in X-linked agammaglobulinaemia.
- Antibody deficiency or other subtle defects secondary to Btk mutation in non-lymphoid cells might possibly contribute to increased susceptibility to tumours, although further work needs to be done to evaluate this.

presenting cell defects or that this is a chance finding (although both XLA and DFSP are very rare).

Conclusion

This is the first case report of DFSP in a patient with XLA. Apart from bronchiectasis, our patient has remained well with no other malignancy. It is possible that in addition to T cells, other factors resulting from a Btk mutation might have a role in immunity against cutaneous sarcomatous tumours, although further evidence would be required to confirm this. As the number of surviving patients with XLA increases because of better treatment, it is possible that more patients with this association might be seen in the future.

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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).