Chronic intestinal pseudo-obstruction (CIP) represents a particularly difficult clinical challenge. It is a rare and highly morbid syndrome characterised by impaired gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions occluding the gut lumen. CIP can be classified as either "secondary" to a wide array of recognised pathological conditions or "idiopathic" (CIIP). This review will focus on CIIP, and specifically on the underlying pathological abnormalities. Combined clinical and histopathological studies are needed to highlight new perspectives in the understanding and management of chronic intestinal pseudo-obstruction.

SUMMARY
The histopathology of chronic intestinal pseudo-obstruction has been frequently reported as a frustrating experience by gastrointestinal pathologists. Renewed interest in gut neuromuscular pathology has been fuelled by the availability of full thickness biopsies obtained with minimally invasive surgical techniques, improvement in tissue preservation, and refinement of a number of morphofunctional techniques. Pathological abnormalities underlying chronic idiopathic intestinal pseudo-obstruction can be classified into three major entities: neuropathies, "mesenchymopathies" (that is, changes in interstitial cells of Cajal network), and myopathies. Inflammatory/immune mediated neuropathies are characterised by either a predominant T cell (CD4 and CD8 lymphocytes) or eosinophilic infiltrate within the myenteric plexus. Other forms of neuropathies are characterised by loss of neurons together with evidence of neurodegenerative aspects in the absence of an identifiable inflammatory response. Abnormalities of interstitial cells of Cajal and smooth muscle cells may also contribute to gut dysmotility. Combined clinical and histopathological studies will open new perspectives in the understanding and management of chronic intestinal pseudo-obstruction.

CHRONIC INTESTINAL PSEUDO-OBSTURATION: A GENERAL OVERVIEW ON A RARE DISEASE
Digestive motility is a highly coordinated process which enables mixing, absorption, and propulsion of the ingesta through the gastrointestinal tract up to expulsion of residues. This function depends on smooth muscle contractility and the related pacemaker activity evoked by the interstitial cells of Cajal (ICCs), both finely tuned by intrinsic (that is, the enteric nervous system (ENS)) and extrinsic (that is, sympathetic and parasympathetic) nerves. Disturbances in digestive motility can occur as a result of a variety of abnormalities affecting each of these elements (alone or in combination) involved in the physiology of gut motor function.

"Intestinal pseudo-obstruction represents a particularly difficult clinical challenge"

Intestinal pseudo-obstruction represents a particularly difficult clinical challenge. It is a rare and highly morbid syndrome characterised by impaired gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions occluding the gut lumen. Pseudo-obstructive syndromes may be either acute (due to abdominal surgery, retroperitoneal haemorrhage, spinal or pelvic trauma, myocardial infarction, or hypokalaemia) or, more commonly, chronic. The latter form (that is, chronic intestinal pseudo-obstruction (CIP)) is an important cause of chronic functional intestinal failure. CIP can be further classified as either "secondary" to a wide array of recognised pathological conditions or "idiopathic" (CIIP). Although familial forms with autosomal dominant or recessive modes of inheritance have been reported, most cases of CIP appear to be unrelated to familial clusters and therefore are referred to as sporadic forms. This review will focus on CIIP, and specifically on the underlying pathological abnormalities.

CLINICAL AND DIAGNOSTIC FEATURES
CIIP patients present with recurrent episodes of abdominal pain, nausea and/or vomiting, and distension and/or bloating mimicking a mechanical sub-occlusion. Diarrhoea and steatorrhoea may occur as a result of bacterial overgrowth of the small intestine. Dysphagia is present in a low percentage of patients with CIIP although it is relatively frequent in those affected by pseudo-obstruction secondary to progressive systemic sclerosis. Nausea, vomiting, and weight loss are

Abbreviations: ANNA-1, antineuronal nuclear antibodies; BCL-2, B cell lymphoma 2; CIP, chronic intestinal pseudo-obstruction; CIIP, chronic intestinal idiopathic pseudo-obstruction; ICC, interstitial cells of Cajal; ENS, enteric nervous system
NEUROMUSCULAR DYSFUNCTION

Damage to the functional and/or structural integrity of the ENS plays a major role in gut dysmotility. This is due to the high morphofunctional complexity of the ENS which is able to control, independently from the central and peripheral nervous systems, virtually all gut functions, including motility. Neurpathic CIP can be classified into two major forms: (a) inflammatory neuropathies in which a significant inflammatory/immune response is identified within enteric ganglia and/or nerve processes; and (b) degenerative neuropathies characterised by evidence of neurodegenerative aspects in the absence of an identifiable inflammatory response.

"Damage to the functional and/or structural integrity of the ENS plays a major role in gut dysmotility"

Inflammatory neuropathies are characterised by a dense infiltrate of lymphocytes and plasma cells involving either of the two major ganglionated plexuses, although mainly the myenteric plexus (that is, myenteric ganglionitis) and axons of the ENS. Usually, cases of myenteric ganglionitis are secondary to several diseases, including paraneoplastic (for example, small cell carcinoma, carcinoïd, neuroblastoma, and thymoma), infectious (for example, Chagas' disease), neurological (for example, encephalomyeloneuropathy), connective tissue (for example, scleroderma), and inflammatory bowel disorders (for review see De Giorgio and colleagues). Nevertheless, some cases may be idiopathic in origin. Immuno histopathological analysis shows an immune infiltrate composed of predominant CD4 (T helper) and CD8 (T suppressor) lymphocytes (fig 1) which can be identified in idiopathic and secondary forms of myenteric ganglionitis. Lymphocytic myenteric ganglionitis is often associated with neuronal changes indicative of degeneration and loss up to complete ganglion cell depletion occurring in the most severe forms (a feature referred to as acquired ganglioneuropathy). In addition to cell mediated immune injury, patients with lymphocytic myenteric ganglionitis develop a humoral response characterised by antineuronal antibodies, namely antineuronal neuronal antibodies (ANNA-1) or anti-Hu (from the name of the molecular target recognised by these autoantibodies). Detection of ANNA-1-anti-Hu antibodies in the serum of patients with idiopathic myenteric ganglionitis is useful for diagnosis and helps to establish the rationale for appropriate immunosuppressive treatment. By contrast, recent data showed a predominant eosinophilic infiltrate in the myenteric plexus of paediatric cases of CIP which does not appear to be associated with overt neurodegeneration.

Degenerative non-inflammatory neuropathies may occur as a result of endogenous and/or exogenous noxae leading to damage and loss of enteric neurones. Typical neuropathological findings include marked reduction of intramural (especially myenteric) neurones associated with swollen cell bodies and processes, fragmentation and loss of axons, and

patients with a permanent catheter for enteral or parenteral nutrition.
proliferation of glial cells. Remaining neurones may be enlarged with thick clubbed processes and associated with an increased number of Schwann cells and hypertrophy of the muscularis propria. Although several studies have focused on increased number of Schwann cells and hypertrophy of the enlarged with thick clubbed processes and associated with an programmed cell death/apoptosis in CIIP tissues.

ALTERATIONS IN THE ICC NETWORK

Alterations in the ICC network have been reported in patients with CIIP.23–25 Electron microscopy and/or KIT immunolabelling combined with confocal microscopy and image analysis demonstrated a quantitative decrease in ICCs along with structural abnormalities such as loss of processes and damaged intracellular cytoskeleton and organelles. The evidence of significant changes in the ICC enteric network further illustrates the critical role played by these non-neuronal cells in regulating gut motility.24–27

FUTURE PERSPECTIVES

Although interesting, these results should be interpreted with caution. Firstly, this study showed that α-actin may undergo complex post-translational processing as its expression also appears to be deficient in the control ileum. This raises two questions: one is about the risk of false positive results due to inappropriate sampling during surgery and the other pertains to the specificity of α-actin immunoreactivity. Secondly, some of the cases with α-actin abnormalities were defined as neurogenic forms of CIIP, thus providing a conceptual gap on the clinical correlate of α-actin changes. Thirdly, CIIP is a heterogeneous syndrome and most histopathological features (that is, nerve, muscle, and ICC abnormalities) may co-exist at the tissue level and contribute synergistically to severe dysmotility. Further studies based on α-actin assessment with western blotting (to identify conformational changes in the α-actin molecule) and/or polymerase chain reaction (to identify possible α-actin altered expression) are needed to clarify the meaning of abnormal α-actin staining and its association with CIIP.

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What is the diagnosis?

Question

polyp was biopsied and fig 1B shows the microscopic features.

scopic decompression was performed. Colonoscopy showed obstruction (Ogilvie’s syndrome) was suspected and colonoscopic decompression was performed. Haematuria resolved but the patient experienced postembolisation syndrome with fever, and presented with bowel obstructive symptoms. Abdominal radiographs showed marked dilatation of the colon. An acute colonic pseudo-obstruction was suspected and colono-

REFERENCES


EDITOR’S QUIZ: GI SNAPSHOT

Unusual complication of tuberous sclerosis complex

Clinical presentation

A 39 year old man with a known history of tuberous sclerosis complex (TSC) presented with haematuria due to haemorrhagic changes of a large renal angiomyolipoma. Selective transcatheter arterial embolisation of the lesion was performed. Haematuria resolved but the patient experienced postembolisation syndrome with fever, and presented with bowel obstructive symptoms. Abdominal radiographs showed marked dilatation of the colon. An acute colonic pseudo-obstruction (Ogilvie’s syndrome) was suspected and colonoscopic decompression was performed. Colonoscopy showed dilatation of the colon without mechanical obstruction and multiple sessile polyps localised in the rectum (fig 1A). One polyp was biopsied and fig 1B shows the microscopic features.

Question

What is the diagnosis?

See page 1565 for answer

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Figure 1 (A) Endoscopy of the colon. (B) Microscopic examination of a biopsied polyp.
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