





# Myotonic dystrophy type 1 and pseudo-obstruction in a child with smooth muscle $\alpha$ -actin deficiency and eosinophilic myenteric plexitis

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## ABSTRACT

Myotonic dystrophy (MD) frequently involves the gastrointestinal tract, where it can manifest as chronic intestinal pseudo-obstruction (CIPO), particularly in adults. This manifestation is quite uncommon in children. We report the case of a 12-year-old boy with MD type 1 and CIPO, in which a pathologic assessment revealed an association with smooth muscle  $\alpha$ -actin deficiency in the external muscular layer of the ileum, and with features of eosinophilic plexitis and eosinophilic muscle infiltration in the colon. In this peculiar case, the clinical aspects of CIPO might have been due to the involvement of several neuromuscular mechanisms.

**Keywords:** Child, eosinophils, myenteric plexitis, myotonic dystrophy, pseudo-obstruction, smooth muscle  $\alpha$ -actin

## INTRODUCTION

Myotonic dystrophy (MD) type 1 is a neuromuscular disorder having several clinical phenotypes (congenital, childhood-onset, adult-onset, and late-onset forms) and a broad clinical spectrum (1). The gastrointestinal tract is often involved in patients with MD, and digestive symptoms may be the first sign of dystrophic disease and may precede the musculo-skeletal features (2).

Lower gut involvement may cause chronic intestinal pseudo-obstruction (CIPO). Most cases of CIPO in MD have been described in adults and in only three instances in children, but histological abnormalities were not reported in two of these latter cases. However, in adults, either no or subtle histologic alterations in the smooth muscle in patients with MD type 1 have been documented (3).

We report the unique case of a child with MD type 1 having CIPO associated with eosinophilic myenteric plexitis and smooth muscle  $\alpha$ -actin deficiency.

## CASE PRESENTATION

A 12-year-old boy with a previous diagnosis of congenital MD type 1 (cytosine-thymine-guanine triplet expansion in the 3'-nontranslated region of the dystrophin protein kinase gene) was admitted in November 2016 because of symptoms of bowel obstruction after complaining of abdominal pain, vomiting, and diarrhea for 2 days. His past medical history revealed three previous hospital admissions elsewhere (April and December 2013 and January 2014) where surgery was performed for intestinal obstruction, but no surgical or histological documentation was available. The patient was irritable and presented with vomiting, abdominal distention, abdominal tenderness, and absence of bowel sounds. Blood chemistry analysis revealed increased C-reactive protein levels and mild elevation in liver enzyme and hemoglobin level. The white blood cell count (including eosinophils), red blood cell count, and platelet number were within normal limits. A plain abdominal X-ray revealed severe small and large bowel distention without pneumoperitoneum.

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(Figure 1). Explorative laparoscopy showed distention of the terminal ileum and colonic volvulus of the ascending colon. Immediately after volvulus detorsion and suction of a liter of chylous effusion, multiple full-thickness ileal and ascending colon biopsies were obtained. One week later, the appearance of toxic megacolon required venting ileostomy to be performed. The subsequent period was uneventful.

The patient's histological assessment revealed mild inflammatory changes in the mucosa, normal aspects of the myenteric plexus in the ileum (Figure 2a and b), and the presence of eosinophils in the muscularis propria and myenteric plexus (myenteric plexitis) within the large bowel (Figure 2c and d). Plexitis was graded as mild (presence of  $\leq 4$  eosinophils penetrating, apportioned to, or within an enteric ganglion) according to previously published criteria (4). No additional feature of plexitis (lymphocytic infiltration) and of smooth muscle degen-

eration, such as fibrosis or vacuolization, was present. Immunohistochemical staining for elements of the enteric nervous system (neuron-specific enolase, S100, and c-Kit; Leica Biosystem, Milan, Italy) was normal in both intestinal segments, whereas staining for  $\alpha$ -smooth muscle actin revealed no expression in the circular layer of the small bowel (Figure 2e and f) and normal expression in the muscular layers of the colon.

Written informed consent to publish this case was obtained from the child's parents.

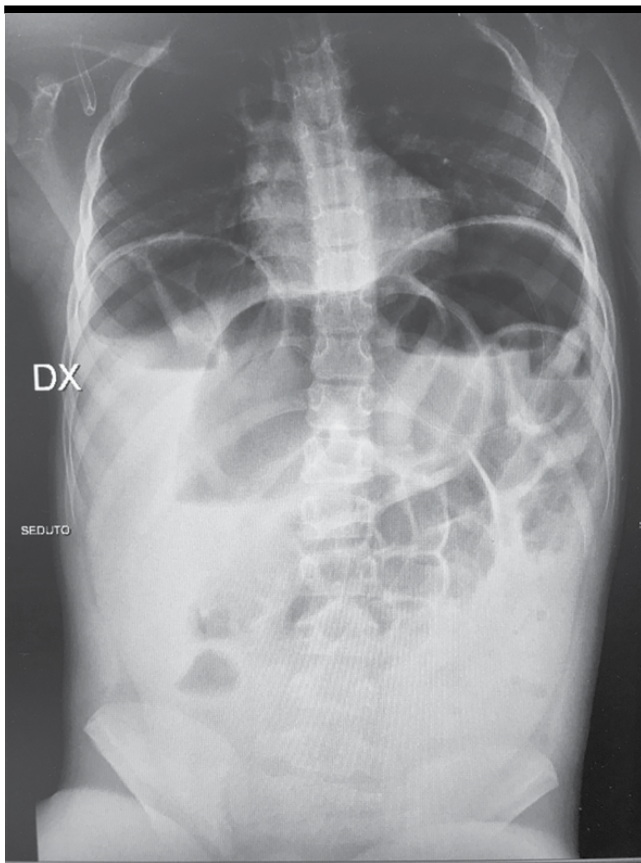
### DISCUSSION

Although MD is characterized by myotonic phenomena and progressive muscular weakness, multisystem involvement (endocrine, cardiovascular, and ocular abnormalities; cognitive impairment; and mental retardation) is frequent (1). The gastrointestinal tract is also commonly involved, particularly having motility abnormalities occurring from the esophagus to the anus (2). Of interest, there is scarce correlation between skeletal muscle damage and gastrointestinal disturbances, whereas the severity of gut involvement and the duration of disease duration are usually correlated (1-3).

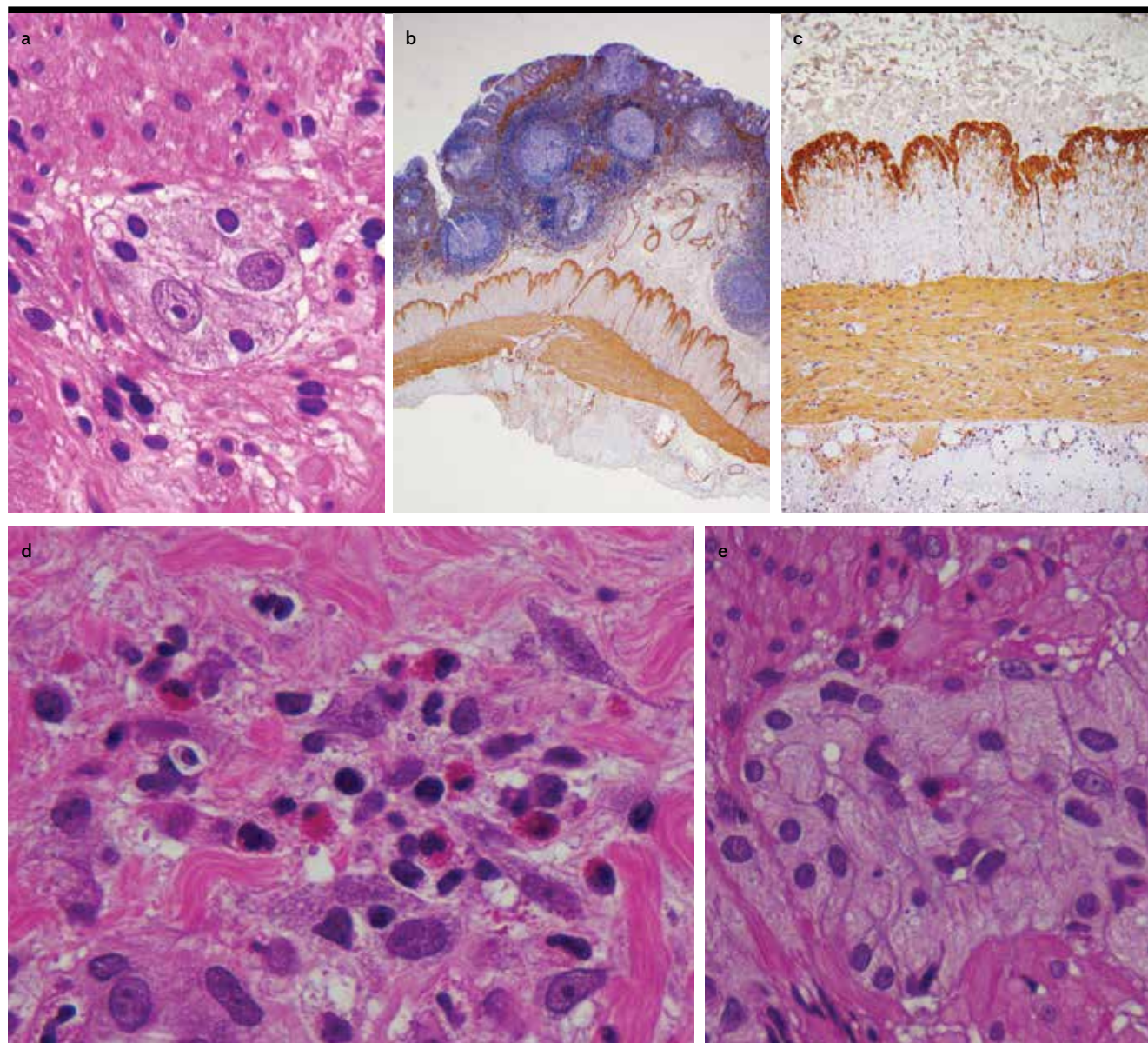
Histologic smooth muscle abnormalities are poorly documented in MD, and it has been hypothesized that such an involvement might precede changes in striated muscles. Some studies have suggested that neurological abnormalities or visceral neuropathy involving substance P and enkephalin-immunoreactive fibers of the smooth muscle play a role (2,5-6).

While combinations of neuropathic, mesenchymopathic, and myopathic changes in cases of CIPO are not uncommon and the loss of  $\alpha$ -actin may be observed in normal tissues, particularly in the terminal ileum, such an association in a patient with MD is a novel observation (7). Although CIPO may be independently due to MD and/or to an abnormal expression of  $\alpha$ -actin and/or to eosinophilic plexitis, these features have never been simultaneously described in the same patient.

The functional significance of  $\alpha$ -smooth muscle actin staining abnormalities in gastrointestinal disease is still unclear. The different levels of  $\alpha$ -isoactin expression in different viscera observed in experimental animal models suggest a functional effect of such changes (7). Alterations in contractile proteins might influence motility, although the effects of a change in smooth muscle



**Figure 1.** Plain abdominal radiograph in the upright position. Severe gaseous distension of numerous loops in the small and large bowel is shown



**Figure 2. a-e.** Small bowel normal ganglion cells in the myenteric plexus. Hematoxylin and eosin (H&E) staining, original magnification: 100 (a);  $\alpha$ -actin immunostaining, original magnification: 4 $\times$ , 20 $\times$  Colon (b, c); eosinophils in the muscularis propria. H&E staining, original magnification: 100 $\times$  (d); eosinophils within the myenteric plexus, H&E staining, original magnification: 100 $\times$  (e)

$\alpha$ -actin alone should be less profound than that of other significant cytoskeletal or structural abnormalities. Of interest, as shown in experimental animal models, low-grade inflammation limited to the mucosa may modulate actin expression, and this immunomodulation can persist after the initial stimulus is removed; this condition may thus impair intestinal motor activity (8). Impaired smooth muscle  $\alpha$ -actin expression has been reported to be a valuable biomarker of CIPO in clinical practice.

In addition, as the enteric nervous system is not altered, the muscular component is likely to have played an important role, together with eosinophilic plexitis (a well-known cause of CIPO that might affect neuroenteric functions) and further muscular impairment by eosinophilic infiltration (9). These abnormalities may have caused volvulus, which is an infrequent complication of CIPO, even though eosinophilic plexitis, which occasionally occurs in Hirschsprung's disease, might have been

a secondary phenomenon to the obstruction caused by volvulus (10,11).

In the present peculiar case, the clinical aspects of CIPO might have been due to several possible causes associated with neuromuscular dysfunction. The relationship between MD, gastrointestinal motility, and symptoms must be always carefully investigated. Histologic aspects and immunohistochemical assessment should be included in the diagnostic work-up of each case to improve the knowledge of basal mechanisms underlying gastrointestinal involvement in MD and possible associations with other pathological conditions and to propose new therapeutic perspectives to manage this difficult condition in a more targeted manner.

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