The association of protein-losing enteropathy, sideropenic anemia, finger clubbing (Herbst triad) and Sandifer syndrome (reflux oesophagitis and head cocking) represents an unusual manifestation of gastro-esophageal reflux disease (GERD). Herein we report a patient presenting this complex clinical picture and, in addition, allergic asthma and allergies to several foods. The surgical correction of the gastro-oesophageal reflux resolved the reflux itself and related symptoms.

**Key words:** Sandifer syndrome, Herbst triad, gastro-esophageal reflux disease

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**Introduction**

Gastro-esophageal reflux is defined as the backflow of gastric contents into the esophagus. To a limited degree, its occurrence without associated symptoms is considered to be a physiological phenomenon. An increase in rate, quantity and duration is generally associated to symptoms and/or anatomical lesions and this generates the condition of gastro-esophageal disease (GERD); it can be primary or secondary to various diseases such as food allergy, metabolic disease, central nervous system abnormalities.

GERD, in paediatric patients, is a condition that usually responds to therapy with protonic pump inhibitors, while surgical correction is rarely required. An unusual clinical presentation of GERD is the Sandifer syndrome, a combination of gastro-oesophageal reflux disease with spastic torticollis and dystonic body movements with or without hialtal hernia.

The association of GER with finger clubbing, sideropenic anaemia and hypoprotidemia is much rarer and it is called Herbst triad: the first three cases were described in 1976, and, subsequently, 2 further cases by Sacher, in 1990. We report the case of a patient suffering from GER, Sandifer syndrome, protein-losing enteropathy, persistent anaemia and finger clubbing, whose GER and associated symptoms only regressed after surgical correction of the reflux.

**Clinical case**

The patient was an 8 years old boy, who had epigastralgia and pyrosis, (mainly postprandial), vomiting, sometimes several times a day, drooling, rumination, head tilting, particularly after meals, reduced growth, decreased appetite and playing activity. Before arriving to our department, the patient had undergone an esophagus-gastro-duodenoscopy (EGDS), which had shown, macroscopi-
cally, a bleeding esophageal mucosa and ulcerative lesions and mild duodenitis. Histologically, at the esophageal level, we found an extensively ulcerated mucosa, granulation tissue permeating the epithelium and chronic inflammation.

In addition, chronic first degree duodenitis was demonstrated. The child was treated with cisapride 0.2 mg/Kg/every 8 hr and ranitidine 5 mg/Kg/every 12 hr and then with omeprazole 20 mg daily, with a partial improvement.

The esophageal 24 hours pH measurement recorded a reflux index of 38%, 18 long-lasting reflux episodes (> 5 minutes) with the longest reflux episode of 60 minutes; the second EGDS was unchanged. The histology of the sample obtained during the first colonoscopy, performed elsewhere, suggested the presence of IBD on the basis of moderate lympho-plasma cellular infiltration of the tunica propria mucosa, where neutrophil and eosinophil nodular aggregation with occasional cryptitis were present.

On admission, the patient, was in fair general condition, he was pale, and the abdomen was tender to palpation in the epigastric area and in the lower quadrant. Finger clubbing was present. On admission he had a weight of 26.6 Kg (50th percentile) and a height of 129 cm (50th percentile). Laboratory tests showed Hb 8.9 g/dl MCV 74 fl, WBC 4700/mmc with hypereosinophilia (700/ml), alfa-1-fecal antitrypsin 23 mg/dl, total serum protein 4.5 g/dl, absence of proteinuria, serum iron 13 mcg/dl, ferritin < 5 ug/dl. The inflammation indexes were within normal limits. Iron absorption test was normal.

Repeated stool searches for occult blood were positive in only two occasions. Stools were negative for viruses, parasites and bacteria. Intestinal permeability test to lactulose/mannitol ratio was 0.067. Sweat test and ANCA were normal. Total IgE 2455 UI/ml, allergen-specific IgE positive for many different kinds of food (peanut 66.2 KUA/L, cod 49.3 KUA/L, lobster 24.7 KUA/L, and mild positivity to many other foods), prick by prick positive for celery. Intestinal scintigraphy with marked leukocytes and a upper gastrointestinal series with small-bowel follow-through were normal.

The second colonoscopy did not allow a complete visualization of the colonic mucosa because of poor intestinal toilet, but the stool free segment appeared to be normal. Microscopically, a mild chronic lymphoplasmacellular infiltration was documented.

The patient was given a high-protein and elimination diet in accordance with the results of allergen-specific IgE, and was treated with omeprazole 40 mg/daily, disodium chromoglycate 250 mg/8 hr and iron at first i.v. and then per os.

After about two months of medical and dietary treatments the child improved but hypoprotidemia and iron deficiency anemia persisted with serum protein values ranging from 4.5 g/dl and 5.8 g/dl and Hb from 5.9 g/dl and 9.3 g/dl.

A follow-up EGDS showed a total regression of the ulcerative lesions and of inflammation in the esophageal and gastric mucosa. Histologically chronic esophagitis with eosinophilic granulocyte infiltration of the esophageal mucosa (59 hpf) and at cardias level (21 hpf) was present. The duodenal biopsy demonstrated regular villi and mild lymphoplasmacellular infiltration of the tunica mucosa.

Based on the histological findings and on the partial response to the therapy with protonic pump inhibitors, eosinophilic esophagitis was suspected and an elementary diet was suggested but his parents refused. Hence oral prednisone at the dosage of 1.5 mg/kg/day was started and omeprazole 40 mg/daily were continued, but gastric discomfort and lack of appetite worsened and therefore corticosteroid therapy was discontinued. At this point, given the lack of response to the therapeutic trials, the patient underwent a surgical procedure of reflux correction (Tupet funduplication).

Five months later, all laboratory and clinical tests were normal and regression of finger clubbing was observed. Growth resumed to normal levels with weight and height at the 75th percentile; Hb, MCV, serum iron, ferritin and serum proteins were normal, while the RAST remained abnormal for some foods and modest hypereosinophilia (558/mmc) persisted. Three years after surgery, the child is asymptomatic, he enjoys a free diet and shows a regular growth. All laboratory tests remain within the normal range.

Discussion and conclusions

In our patient, the complex clinical picture caused some diagnostic difficulties in differentiating the condition from eosinophilic esophagitis and chronic inflammatory bowel disease (IBD). The eosinophilic infiltration of the esophageal mucosa and its partial response to therapy with omeprazole seemed to support the diagnosis of eosinophilic esophagitis.
This diagnosis must be taken into consideration every time the symptoms suggesting a GER disease do not respond to therapy with protonic pump inhibitors, especially if the patient has a personal or family history of allergy. The histologic finding of an eosinophil count in the upper esophageal mucosa higher than a 20 per hpf is diagnostic for eosinophilic esophagitis\(^7, 8, 10\). The hypothesis that all signs, symptoms and laboratory abnormalities, presented by our patient, were due to gastroesophageal reflux disease is supported by the complete resolution of symptoms only after a reflux surgical correction. This does not support a diagnosis of eosinophilic esophagitis\(^10\). Also, the patient remains symptomless three years after surgery without any therapy.

Gastro-esophageal reflux and esophagitis could be associated with hypertrophic osteoarthropathy\(^2\). The physiopathological mechanisms causing finger clubbing are still incompletely understood. It can appear as an isolated sign or in association with chronic proliferative periostitis and synovitis, forming the clinical picture of hypertrophic osteoarthropathy. It is often associated with a number of pulmonary, cardiac, gastrointestinal, infectious, endocrine, and multisystem diseases. Most microscopic and imaging studies of clubbed fingers reveal hypervascularization of the distal digits.

Recent research shows that when platelet precursors fail to become fragmented into platelets within the pulmonary circulation, they are easily trapped in the peripheral vasculature, releasing platelet-derived growth factor and vascular endothelial growth factor, promoters of vascularity and, ultimately, clubbing\(^11\).

The long follow-up without symptoms and normalization of laboratory abnormalities in the absence of any pharmacological or dietary therapy suggests that in our patient a severe gastro-oesophageal reflux was responsible for the entire clinical picture, including the protein-loss and anaemia.

Iron deficiency, in fact, appears to damage the jejunal mucosa causing hypoprotidemia\(^1, 5, 6\) and an inability to absorb iron, starting a vicious circle that leads to persistent anemia.

References