promise for these patients and their families but still awaits dedicated investigations in larger series of patients to determine its place in the paediatric surgeon's armamentarium.

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Secondary amyloidosis in Crohn's disease: treatment with tumour necrosis factor inhibitor

We present the case of a 26 year old male patient diagnosed with ileocolonic Crohn's disease at age 15 years, with a history of several episodes of perianal inflammation that required surgical debridement. In 2000, he was hospitalised for tibio-malleolar oedema that had appeared progressively over the previous four months, associated with clinical signs of perianal inflammation and anal pain after defecating.

Physical exploration revealed a patient who was generally well, with a cushingoid appearance, pallor of skin and mucosae, oedema with fovea in both lower extremities up to the knee, minimum (not painful) fullness of the lower right quadrant and, on anal exploration, three uncomplicated "strings" with a suppurating point adjacent to one of them.

Laboratory tests showed $17\,720 \times 10^6$ leucocytes (11 600 neutrophils), haemoglobin 9.8 g/dl, platelets $577\,000 \times 10^6$ /l, cholesterol 294 mg/dl, triglycerides 197 mg/dl, total blood proteins 4.9 g/dl, albumin 2.4 g/dl, sedimentation velocity 122 mm,¹ β_2 -microglobulin 3.8 mg/l, urea 48 mg/dl, creatinine 1.7 mg/dl, fibrinogen 10.48 g/l, and negative antinuclear antibodies. He had an inactive urinary sediment, a creatinine clearance of 71 ml/dl, and proteinuria of 8 g/dl (selectivity index 0.22), which reached 20 g/24 h after a few days.

Abdominal Doppler ultrasound showed ileal disease, without local complications, and the small intestine follow through study showed two fixed and spiculated ileal loops. Renal ultrasound was normal.

The nephrotic range proteinuria in a patient with Crohn's disease made us suspect secondary amyloidosis. Colonoscopy was performed to evaluate intestinal inflammation as well as rectal biopsy to rule out amyloidosis. Rectal biopsy was positive for Red

Congo, which confirmed the suspected diagnosis (fig 1).

Treatment with Infliximab and azathioprine (100 mg/day) was indicated because of the severity of the perianal disease, which had not responded to conventional treatment. The patient received an anti-tumour necrosis factor α (TNF- α) infusion at weeks 0, 2, and 6, and every two months thereafter for four years. Colchicine is the empirical treatment for amyloidosis.

Perianal disease inflammation remitted completely and proteinuria began to decrease. Proteinuria values were 4 g/24 h after one year of treatment and 0.82 g/24 h after four years of treatment. The patient was treated with the three drugs (Infliximab, azathioprine, and colchicine) for the first four years and then with Infliximab for the last year (fifth year of treatment). Although asymptomatic, rectosigmoidoscopy to obtain new biopsies was performed after four and five years of treatment. The mucosa was macroscopically normal and biopsies were only slightly positive for Red Congo (there were a few irregularly distributed amyloid deposits) (fig 1) and positive on immunohistochemistry for substance P.²

To date, there has been no effective treatment for secondary amyloidosis^{3–5}; treatment consisted of treating the underlying inflammatory disease.^{2,6,7} This case is interesting because, when treated with Infliximab, there was an important clinical and analytical improvement, apparently followed by a decrease in the degree of Red Congo stain for amyloid deposits.

The clinical improvement in Crohn's perianal disease and the kidney abnormalities caused by amyloidosis (with an evident decrease in proteinuria values), as a response to the immunomodulating drugs, was remarkable, but even more so the fact that less amyloid deposits were seen in the second and third rectal biopsies.^{8,9}

Further study is required to confirm the relationship between treatment and clinical improvement¹⁰ and to determine if the combination of the three drugs is necessary (immunosuppressor (azathioprine) + immunomodulator (Infliximab), and an anti-inflammatory drug (colchicine)), or if

Figure 1 Red Congo stain before (A, year 2000) and after (B, year 2005) five years of treatment.

anti-TNF- α alone is effective. Clinical improvement with Infliximab has been reported in two cases of proteinuria due to secondary amyloidosis in Crohn's disease. However, they did not show the significant improvement in proteinuria and anatomic-pathological parameters observed in our patient.

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The stomach periglandular fibroblast sheath: all present and correct

We were interested in the paper by Mutoh and colleagues¹ showing the development of epithelial intestinal metaplasia and mesenchymal proliferation in human stomach

resections and Cdx2 transgenic mice. The authors used α smooth muscle actin (α -SMA) staining to mark periglandular fibroblasts and failed to show any α -SMA positive cells surrounding the en face glands of normal mouse and human stomach mucosa. In metaplastic tissue however, the periglandular fibroblast sheath was easily discernible, and the authors concluded that the fibroblast sheath was generated from the intestinal submucosa, possibly through expression of Cdx2.

Mesenchymal cells such as intestinal subepithelial myofibroblasts (ISEMF) are widely distributed. They are important coordinating

cells that possess significant influence on their environment by virtue of their receptor profile and the signals they produce. Characteristically, ISEMF form a protective fenestrated sheath around the stem cell compartment, creating the stem cell niche—the optimal microenvironment for stem cells to give rise to differentiated progeny.² The stem cell niche is situated in the isthmus/neck region of the gastric gland. ISEMF regulate stem cell behaviour via paracrine secretion of growth factors and cytokines, and perform vital functions in the growth, differentiation, and development of the embryological stomach. They participate in

Figure 1 The normal stomach periglandular fibroblast sheath (PGFS). (A) Human α smooth muscle actin (α -SMA) control. (C) Human vimentin control. Normal human gastric glands counterstained with haematoxylin (40 $\times$ magnification). (B) α -SMA immunostaining. (D) Vimentin immunostaining. Normal human gastric glands with surrounding PGFS (brown stain) embracing the epithelial cells of the gastric glands (40 $\times$ magnification). (E) Mouse α -SMA control. Normal mouse gastric glands counterstained with haematoxylin (40 $\times$ magnification). (F, G) α -SMA immunostaining. Normal mouse gastric glands in en face (F) and cross sectional (G) orientation showing the close association of the PGFS (brown stain) surrounding and enveloping the normal stomach glands (60 $\times$ magnification).