

COLLAGENOUS COLITIS: POSSIBLE LINK WITH ISOTRETINOIN

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SUMMARY: A case of collagenous colitis in a young man treated by isotretinoin raises the hypothesis of an isotretinoin induced, auto-immune process on the possible account of atopy and auto-immunity in the family.

CLINICAL CASE

A 26-year old man presented in December 2004 with gastro-intestinal symptoms after treatment with isotretinoin (Roaccutane®: 0.5 mg/kg) for facial acne. Treatment was started in December 1999 and withdrawn in July 2000 because of pharyngeal pain and diarrhoea. The man lost 12 kg in the first three months, but his weight subsequently returned to normal. Diarrhoea fluctuated over the following years. Coloscopy was performed in 2001 and findings were normal. No biopsies had been done. Food allergy was considered and various eviction diets were tried without effect.

In December 2004, general condition was good and the clinical examination did not reveal any abnormality. Atopy was documented with his father and sister (allergic rhinitis and asthma). A family predisposition to auto-immunity was represented by a juvenile type 1 diabetes with his sister. He had suffered from asthma in childhood.

A diagnosis of food allergy was ruled out. Investigations for coeliac disease by serology and HLA grouping were negative. Antinuclear antibodies of pseudo-nucleolar type were raised to 1/128th. Tests for p-ANCA and c-ANCA antibodies were negative. Upper alimentary tract endoscopy revealed a grade 1 peptic esophagitis. Coloscopy was normal. Biopsies revealed collagenous colitis (photo 1).

DISCUSSION

Microscopic colitis includes collagenous and lymphocytic colitis that are characterised by chronic diarrhea and inflammatory changes at cellular level, but with normal colonic mucosae on endoscopy. The prevalence of microscopic colitis is estimated at about 10 per 100 000. The aetio-patho-genesis is not known (1, 2). An association with other auto-immune diseases, such as thyroiditis, type 1 diabetes, coeliac disease and rheumatoid arthritis, and with the presence of anti-nuclear and ANCA antibodies, suggests it may be an auto-immune process. Recent cases related to food allergy have been reported (2).



Figure 1: Histology of colonic mucosa: colouration with haematoxyline-eosine-safran (enlargement x 200)

Focal thickening (more than 15 μ) of the basement membrane of colonic mucosa (ranging from 20 to 25 μ). Flaky, homogeneous, eosinophilic appearance. Surface epithelium slightly dystrophic with regular glands, normal muscularis mucosae, discreet lympho-plasmocytic infiltration in the chorion revealing discreet inflammation (Pr E Labouyrie).

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The characteristic feature of collagenous colitis (CC) is a sub-epithelial deposit of collagen (minimal thickness 10 µm). This extra-cellular matrix is composed essentially of type I and III collagen and fibronectin. It undergoes constant fibrolysis by metallo-proteases, particularly collagenases. The study of genes from colonic mucosa of CC has confirmed a high level of tenascin, a mesenchymatous cell-proliferation marker, indicating accelerated turn-over of extra-cellular matrix. These deposits may disappear within a few months. In parallel, a decrease in type I collagenase transcripts was observed, and an increased expression of metallo-protease inhibitors. There appears to be a total imbalance between increased fibrogenesis and deficient fibrolysis (3).

Isotretinoin (Roaccutane®) is a synthetic vitamin A analogue: 13-cis-retinoic acid. It has been incriminated in rare cases of inflammatory intestinal disease within a few weeks, or months, of the start of treatment. The incidence is about 1 case per 10 000 treated patients. No cases of collagenous colitis have been reported in the international pharmaco-vigilance data base of the laboratory (publication by Laboratory Roche). Published case reports reveal the diversity of colonic disorders: ulcerous colitis, acute aphtous recto-sigmoiditis, proctitis, aphtoid colitis with epithelioid granuloma (4-7). Symptoms stopped a few days to four weeks after isotretinoin was withdrawn (4, 6, 7), and re-started when the treatment was re-introduced (4, 7). Isotretinoin is absorbed by gastro-intestinal mucosa, and is metabolised in the liver, where its principal metabolite is 4-oxo-isotretinoin. The drug and its metabolites follow an entero-hepatic cycle. The return to baseline level of retinoids requires about two weeks after treatment withdrawal (8).

Retinoids control cell differentiation and proliferation in epithelia. The synthesis of certain proteins, such as fibronectin, is increased and that of other proteins, such as collagenase and gelatinolytic protease is decreased (9).

This case report raises the possibility of a link of collagenous colitis with treatment with isotretinoin. Symptoms appeared after six months of treatment,

which is longer than for previously published reports. The duration of diarrhoea after treatment withdrawal was abnormally long. However, there are reports of drug-induced collagenous colitis. Riddell demonstrated a significantly more frequent chronic intake of NSAIDs in patients with collagenous colitis than for a control group with irritable bowel syndrome alone (10). Other drugs, ticlopidine and flutamide, have been also incriminated (1, 10).

An auto-immune process is supported by the presence of ACAN for which the limit value appears to be significant for a young man. The hypothesis that this drug may enhance an auto-immune process in a person with a family predisposition to atopy and auto-immunity should be considered.

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