Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions

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Abstract

A considerable number of agents have been proposed as causing ligneous conjunctivitis. We report the first case to arise as a side effect of tranexamic acid (Cyclokapron), an anti-fibrinolytic drug used in the treatment of menorrhagia. In addition to the typical conjunctival changes our patient had lesions affecting the gingiva and the peritoneum the last causing considerable protein loss into the peritoneal cavity.

Ligneous conjunctivitis is a rare form of membranous conjunctivitis of unknown aetiology.¹ The disease classically presents with the appearance of thickened, 'wood-like' membranes covering the tarsal conjunctiva. Other mucus membranes may also become involved, including the middle ear, buccal mucosa, nasopharynx, larynx, vocal cords, trachea, vagina, and cervix.¹⁻⁴ We report a case of ligneous conjunctivitis in a young woman with Epstein's syndrome with involvement both of the gingiva and the peritoneum, caused by tranexamic acid (Cyclokapron).

Case report

In March 1990 a 25-year-old Caucasian woman presented to the Bristol Eye Hospital with a nine-

month history of ocular irritation and sticky discharge. On examination she had swollen eyelids with thickened, pale membranes adherent to the tarsal conjunctiva (Fig 1). Surgical debridement revealed the underlying conjunctiva to be hyperaemic and haemorrhagic, though it was rapidly coated as the membranes reformed. She also had generalised gingival hyperplasia with shallow ulcers predominantly at the gingival margin (Fig 1). Her ears, nasopharynx, larynx, vagina, and cervix were normal.

Three years earlier a diagnosis of Epstein's syndrome had been made after she presented with thrombocytopenia, nephropathy, and sensory deafness. Subsequent renal failure had necessitated peritoneal dialysis. On presentation, systemic drug treatment including daily pindolol 40 mg, enalapril 5 mg, indoramin 150 mg, sotalol 40 mg, alfacalcidol 0.25 mg, tranexamic acid 3 g, and erythropoietin 1500 units twice weekly. The tranexamic acid had been instituted in June 1989 to control menorrhagia. No other drug therapy had been started during the course of her disease.

Histological examination of the conjunctival membranes revealed masses of fibrin with collections of inflammatory cells, plus islands of entrapped epithelial cells (Fig 1). Gingival biopsy revealed hyperkeratosis and reactive thickening with ulceration and pronounced fibrin leakage, oedema, and fibrosis (Fig 1).

Over the following three months topical ocular

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Figure 1 Top left: Gingival hyperplasia with ulceration. Bottom left: Photomicrograph of gingiva, illustrating hyperkeratosis, ulceration, and fibrin deposition. (H-E, $\times 35$.) Top right: Fibrinous membrane adherent to tarsal conjunctiva. Bottom right: Photomicrograph of membrane, showing amorphous fibrinous mass, with entrapped inflammatory cells. (H-E, $\times 265$.)

treatment included antibiotics, corticosteroids, cromoglycate, hyaluronidase, heparin, and cyclosporin. None of these induced any notable improvement.

Throughout this period she suffered a progressively increasing loss of protein into her peritoneal dialysis fluid, which became viscous and occasionally clotted. Quantitative analysis revealed a protein concentration of 0.62 g l^{-1} , with a daily output of up to 2.48 g . Her serum total protein fell to 49 g l^{-1} and her albumin to 20 g l^{-1} causing her to become oedematous and to require albumin infusions. She further developed bilateral corneal ulcers, which proved refractory to treatment and healed only after prolonged occlusion.

In June 1990 all systemic drug treatment was discontinued, since a drug reaction was considered possible. Three weeks later the conjunctival membranes began to disintegrate, and over the subsequent 10 to 14 days they disappeared altogether. Over this same period her peritoneal protein loss resolved, her serum albumin rose to 39 g l^{-1} , and her gingiva returned to normal health.

In September 1990 a recurrence of petechial bruising led to the reintroduction of tranexamic acid treatment. After a total dose of 6 g given over two days the lesions began to form again. No other new drug treatment was instituted at this time. Discontinuation again resulted in full resolution, and in the absence of tranexamic acid her eyes, mouth, and peritoneum have remained healthy.

Discussion

Von Graefe first referred to ligneous conjunctivitis in 1854, though it did not acquire the distinctive name until 1933.⁵ Since that time various aetiological agents have been proposed, including trauma, autoimmune phenomena, hypersensitivity reactions, bacterial or viral infections, and hereditary influences.¹ The underlying pathological abnormality probably involves a vasculopathy with increased vessel permeability and consequent protein loss, mainly fibrin.¹ Such a process has not been reported to involve either the peritoneum or gingiva.

Epstein's syndrome was first described in 1972 as a variant of Alport's syndrome,⁶ a dominantly inherited disorder in which nephritis

is associated with sensorineural deafness. Epstein's syndrome includes these features in association with thrombocytopenia. Recognised ocular features (of Alport's syndrome) include retinitis pigmentosa, cataract, lenticonus, and spherophakia. Ligneous conjunctivitis has not been reported.

In this case the association between ligneous conjunctivitis and exposure to systemic tranexamic acid was confirmed when the condition resolved, recurred, and subsequently resolved during two cycles of drug treatment. Recognised adverse effects of tranexamic acid include a tendency to intravascular clot formation, including stroke.⁷ Ocular side effects include central retinal artery occlusion⁸ and defects in colour vision. High doses in dogs cause retinal degeneration.⁹

The role of tranexamic acid in the aetiology of ligneous conjunctivitis is not apparent. It is possible that a pre-existing vasculopathy resulted in extravascular deposition of fibrin, the lysis of which was subsequently inhibited by the anti-fibrinolytic effect of tranexamic acid. A second postulate could include the tranexamic acid functioning as an antigen or a hapten, with subsequent antigen-antibody complex deposition resulting in complement-mediated vascular endothelial damage and consequent fibrin leakage.

Because tranexamic acid cannot be the aetiological factor in most cases of ligneous conjunctivitis, however, the present case would suggest that this condition may be the clinical expression of a variety of pathological insults.

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