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The Use Of Mycophenolate Mofetil To Treat Mid-Dermal Elastolysis

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Figure Legends:

- 1) Inflamed axilla in mid-dermal elastolysis, prior to treatment with mycophenolate mofetil
- 2) Lax skin of groin in mid-dermal elastolysis

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- 3) Haematoxylin and eosin stain of punch biopsy from groin showing elastophagocytosis (400X magnification)
- 4) CD34 stain of punch biopsy from groin showing increased numbers of CD34 expressing cells (100X magnification)
- 5) Resolution of mid-dermal elastolysis erythema in axilla following treatment with mycophenolate mofetil

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ABSTRACT

Mid-dermal elastolysis is an acquired skin condition affecting the elastin fibers of the dermis, resulting in laxity of the skin. We report a case of mid-dermal elastolysis, where novel treatment with mycophenolate mofetil was successful.

CASE REPORT

A previously healthy 15 year old presented with a 5 month history of red plaques in the bilateral groin and axillae, with associated lax skin. It was rapidly progressive, associated with malaise and nausea. The condition was highly distressing, resulting in school absence, and withdrawal from hobbies and social events.

There was no significant past medical history, no previous dermatoses, including urticaria. There was no family history of autoimmune disease. She did not use any medications regularly, including oral contraceptives. There was no history of tanning bed use or excessive sun exposure.

On clinical examination, red to violaceous reticular cutaneous plaques, with associated laxity were noted in the groin and axillae, (Figures 1 & 2). There were no annular lesions or papular protrusions. There was no hair, nail or joint involvement. Mucous membranes were also unaffected. The eruption was not photodistributed.

Extensive laboratory tests, including anti nuclear antigen, antibodies to extractable nuclear antigen, anti-double stranded DNA and thyroid function were within normal limits.

A skin biopsy was taken. Haematoxylin and eosin staining, showed a normal epidermis, with a dermal infiltration of histiocytes and multinucleated giant cells, with associated elastophagocytosis. There was no necrobiosis or granulomas, no notable solar elastosis and no atypical lymphocytes or epidermotropism (Figure 3).

Initial histological differential diagnosis based on the elastophagocytosis, included mid-dermal elastolysis, granuloma annulare, anetoderma and cutis laxa.

With Verhoeff-van Gieson staining, a reduction in elastic fibers was seen, particularly in the mid-reticular dermis and immunohistochemistry showed increased expression of CD34+ and CD68+ cells (Figure 4), consistent with mid-dermal elastolysis (1, 2).

With no obvious trigger for the disease process and no underlying condition to treat, the patient was commenced on methotrexate, at a dose of 15mg per week, with limited improvement. The disease progressed, with a documented weight loss of 6kg and increasing lethargy, requiring admission to hospital. There was full investigation by the pediatric multi-disciplinary team and no other underlying cause was found. The cutaneous laxity had a notable impact

on the emotional well-being of the patient and regular psychological support was required.

After 4 weeks of methotrexate mono-therapy, prednisolone was added, at an initial dose of 1mg/kg, weaned slowly by 5mg per month.. After 10 weeks methotrexate was changed to hydroxychloroquine at a dose of 200mg twice daily, and two months later dapsone was added at a dose of 100mg daily.

Despite treatment with hydroxychloroquine and dapsone, prednisolone could not be weaned below 15mg/day.

After 6 months, due to the need for an alternative immunosuppressive agent, mycophenolate mofetil (MMF) was trialed, with dosing increased over 6 weeks to 1.5g daily in divided doses. Three months after commencing MMF the cutaneous erythema resolved and the laxity halted (Figure 5). Overall systemic symptoms also improved, enabling a return to pre-morbid function, and prednisolone was able to be fully weaned. MMF was stopped by the patient 11 months later, with no flare documented on ongoing clinical review 9 months post treatment cessation.

DISCUSSION

First described in 1977 mid-dermal elastolysis (MDE) is an acquired skin condition affecting the elastin fibers of the dermis (3). It is primarily seen in young Caucasian women most commonly affecting the trunk and proximal extremities (4). MDE can present in various ways, and there have been three distinct entities described in the literature. Type 1 presents as well-circumscribed fine wrinkles, Type 2 is primarily perifollicular papular protrusions and Type 3 has the feature of persistent reticular erythema and wrinkling (3, 5, 6). Type 1 has been reported to be preceded by erythema with or without burning, which is the most clinically consistent type for this case (3).

The exact pathogenesis of MDE is unknown, but reported triggers include pregnancy, oral contraceptive pills, ultraviolet exposure and smoking (2). There has also been a reported association with Graves' disease, Hashimoto's thyroiditis, systemic lupus erythematosus and rheumatoid arthritis (7). There was no identifiable trigger or association in this case.

MDE is a disease that carries a high morbidity amongst young sufferers, who struggle psychosocially with the lax skin (7).

Systemic symptoms have not been previously reported in MDE and may be explained in this case by the psychological impact of the condition. Formal mental health assessment suggested a diagnosis of anxiety secondary to body image issues. There was no previous anxiety or mental health diagnosis.

Apart from prednisolone, there is currently no known reliably effective treatment for MDE and management often includes supportive care and corrective plastic surgery.

Immunohistological studies and cell culture experiments indicate that imbalances in elastin turnover are associated with pathological degradative processes, including increased elastolytic activity (4). Elastic tissue is degraded by matrix metalloproteinases (MMPs) (8) The catalytic activity of MMPs is controlled by endogenous-specific inhibitors known as serum tissue inhibitors of metalloproteinases (TIMPs) (4) and the balance of TIMPs and MMPs determines the overall elastin loss. An imbalance of MMP/TIMP has been demonstrated in MDE (1, 2, 9, 10). Tajima *et al* (11) found increased synthesis of elastases such as cathepsin G in cultured fibroblasts of MDE patients. The role of MMPs and TIMPs extends beyond that of elastin balance. Both MMPs and TIMPs also act as important cytokines for extracellular matrix synthesis and degradation. They are involved in tissue remodeling and tumour angiogenesis (12), and the expression of MMP-2 and

TIMP-1 is an important molecular mechanism in the development of interstitial fibrosis and rejection following organ transplant (13).

Mycophenolate mofetil (MMF) has been found to reduce the up-regulation of MMP/TIMP which is observed post organ transplant. It has therefore evolved as a first line treatment choice post transplant, for immunosuppression and also to reduce rejection from fibrosis.(14) In the absence of evidence-based literature for treatment of MDE, and with a high burden of disease experienced by this patient, MMF was trialed. Pharmacologically, MMF is the pro-drug of mycophenolic acid (MPA), and is a selective, noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme for guanosine triphosphate synthesis. Inhibition of *de novo* purine synthesis and guanosine nucleotide depletion reduces T and B-lymphocyte proliferation (15). As a purine inhibitor, MMF has broad use for immunosuppression and disease modulation in both dermatological and non-dermatological settings. The rationale for using MMF in this case of MDE was not only as an immunosuppressive agent, but based on its additional ability to alter the MMP/TIMP expression (14). We postulate that MMF acted to regulate the imbalance of elastin in the mid-reticular dermis.

CONCLUSION

MDE is a challenging condition to treat. We present a novel treatment option, with a logical pharmacological explanation to account for its success.

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