

Agminated Blue Naevi in a Patient with EMO Syndrome

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The triad exophthalmus, pre-tibial myxoedema, osteoarthropathia (EMO syndrome) was first described by Thomas in 1933 and represents a rare condition occurring in patients with Graves' disease (1). Graves' disease is a common autoimmune disorder of the thyroid gland due to a production of autoantibodies mainly directed against the thyrotropin (TSH) receptor. In less than 1% of affected patients, the triad of endocrine ophthalmopathy, myxoedema and osteoarthropathy successively occurs in the course of the disease (2–4). We describe here a case of EMO syndrome with agminated blue naevi at both temples suggestive for a Carney complex. Individuals affected by a Carney complex typically present with cardiac and cutaneous myxomas, endocrinopathy, lentiginosis and endocrine and non-endocrine neoplasia (5).

CASE REPORT

A 57-year-old woman was admitted because of slowly progressive acral swelling and skin induration, remarkable growth of hands and feet and loss of sensibility of both hands. The patient had a history of Graves' disease with hyperthyreosis and endocrine ophthalmopathy for more than 20 years and had been subjected twice to subtotal thyroidectomy, with subsequent thyroid hormone substitution therapy. Physical examination revealed a significant exophthalmus of both eyes, swelling of both hands, fingers, lower legs, feet and toes, with particularly affected big toes of both feet

(Fig. 1A, B). The skin of the lower legs appeared to be thickened and fixed to the underlying tissue. In addition, there were multiple aggregated purple papules at both temporal areas (Fig. 1C). The patient had a history of a myxoma located at the mitral valve; however, a recent echocardiography could not confirm any cardiac abnormalities.

Histopathological examination of the skin biopsy specimen from the left big toe revealed a greatly thickened dermis with separation of collagen bundles and a sparse inflammatory infiltrate. Alcian blue staining revealed extensive dermal deposits of mucin throughout the dermal compartment (Fig. 1D). Based on these findings the diagnosis of acral myxoedema was made, which appeared to extend to the lower legs and pre-tibial areas. Histopathological examination of one papule from the left temporal area showed elongated, slightly wavy melanocytes filled with small melanin granules in the dermal tissue. These findings confirmed the diagnosis of agminated blue naevi at both temporal areas. Levels of somatotrophic hormone (STH), STH suppression tests, insulin-like growth factor (IGF-1), as well as thyroid-stimulating hormone levels, were within normal limits. A pituitary adenoma could be excluded by cranial magnetic resonance imaging. An X-ray image of both hands displayed a slight periosteal tissue reaction. Taken together, the diagnosis of EMO syndrome and agminated blue naevi at both temporal areas was made. Pedigree analyses revealed hyperthyroidism affecting



Fig. 1. (A) Acromegaly-like enlargement of feet in exophthalmus, pre-tibial myxoedema, osteoarthropathia (EMO) syndrome. (B) Swelling of hands and digital clubbing. (C) Multiple (agminated) blue naevi at the left temporal area. (D) Extensive deposition of mucin in the dermal tissue of a biopsy taken from the left big toe (Alcian blue staining; original magnification $\times 100$).

several family members, the sister and both daughters having this condition. However, a molecular genetic analysis of the *PRKARIA* gene, which is mutated in 65% of patients with Carney complex (5), showed no evidence of a mutation. Treatment of the pre-tibial myxoedema with hydroxychloroquine was initiated, but was discontinued by the patient. A therapeutic approach with methotrexate had to be stopped due to side-effects. There was no significant clinical improvement within 8 months of follow-up.

DISCUSSION

Elephantiasis based on acral myxoedema is a very rare manifestation of EMO syndrome and was described in only 5 out of 178 cases of dermatopathy associated with Graves' disease (4). The pathogenesis of myxoedema is still poorly understood. Cross-reactive TSH receptor antibodies are supposed to bind to fibroblasts, inducing an autoimmune process. In this inflammatory environment, overproduction of glycosaminoglycans may result from non-specific fibroblast activation (6, 7). Acral osteoarthropathy (acropachy) including digital clubbing has been described as a late manifestation of Graves' disease (3). Acropachy may involve bones, tendons and muscles (7–9).

Treatment of EMO syndrome consists of occlusive application of topical steroids with compression, intralesional and systemic corticosteroids, pentoxifylline, octreotide, methotrexate, photochemotherapy and surgical excision. Further therapeutic approaches include gamma globulin, plasmapheresis and immunotherapy (3, 7, 10). The therapeutic intention aims at a reduction in the fibroblast-induced production of hyaluronic acid. Overall, treatment success for Graves' dermatopathy remains limited.

The co-occurrence of EMO syndrome and agminated blue naevi has not been described up to now. However, thyroid gland abnormalities in combination with spotty skin pigmentation, multiple blue naevi, cardiac and skin myxomas and schwannomas and other non-endocrine and endocrine tumours have been described and termed Carney complex (11). Carney complex is a familial multiple neoplasia disorder genetically transmitted in an autosomal dominant manner. Mutations are located

mostly on chromosome 17q22-24 (*PRKARIA*) encoding for the regulatory subunit of cyclic AMP-dependent protein kinase A ($RI\alpha$). In our patient, this mutation was not present. However, genetic alterations of *PRKARIA* are detected in only approximately 65% of all patients with Carney complex (5). Alternative mutated gene loci leading to the manifestation of a Carney complex-like phenotype have not been identified so far (5). Taken together, an unusual manifestation of EMO syndrome is presented, which may be part of a Carney complex.

The authors declare no conflicts of interest.

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