Case 9

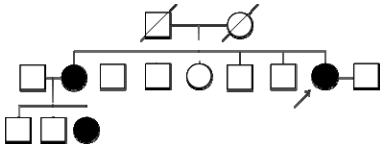
A 41-year-old housewife from Bangkok

Chief complaint: Chronic, pruritic, brownish patch on upper back.

Present illness: The patch, first noticed 16 years ago, gradually spread over time. Due to a positive family history of multiple endocrine neoplasia type 2A (MEN2A), she was tested for and diagnosed with MEN2A 1 year ago, consisting of medullary thyroid carcinoma (MTC) and pheochromocytoma of the left adrenal gland.

Past history: Diabetes mellitus for 1 year.

Family history: Eldest sister (fig. 2) and her daughter (fig. 3), both with MEN2A (MTC, parathyroid adenoma, and pheochromocytoma), had similar lesions on upper back since their mid-twenties. Other 5 siblings were tested negative for RET proto-oncogene mutation.

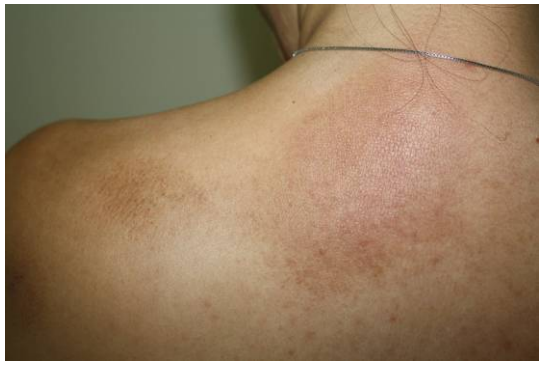


Skin examination: Multiple, small, non-scaly, brownish macules, arranged in a rippled pattern and coalescing to an ill-defined brownish patch on upper back (fig. 1).

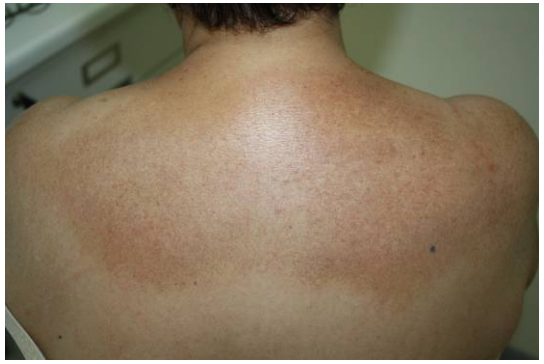
Histopathology (S11-10912)

Multiple pale amphophilic globues with some melanophages at the dermal papillae

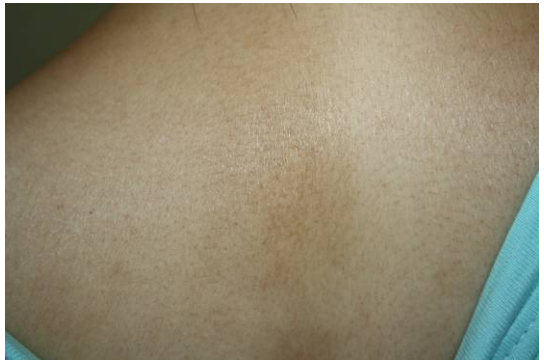
Mild hyperkeratosis and hyperplasia with occasional dyskeratotic cells



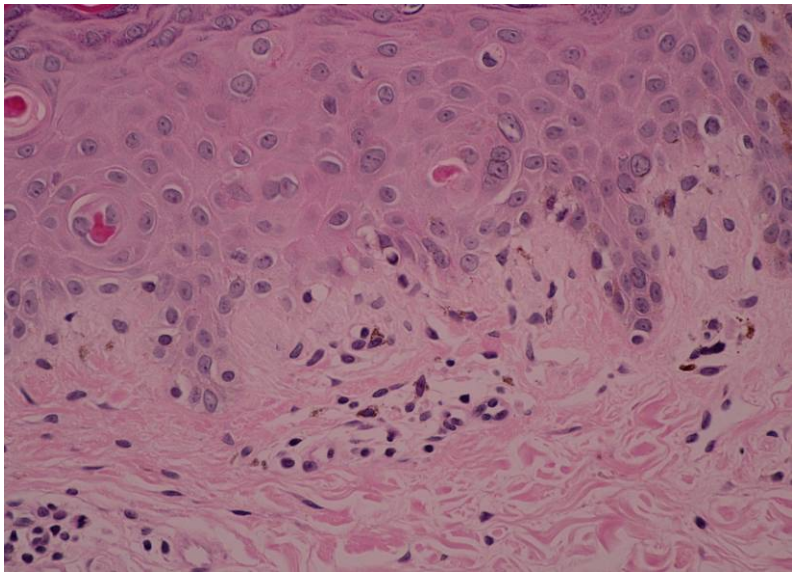
(fig. 1)



(fig. 2)



(fig. 3)



Investigation: CBC, BUN, Cr, LFT, PTH, Ca, PO_4 - normal. Heterozygous mutation of Cys634Tyr in exon 11 of RET proto-oncogene in all 3 cases.

Diagnosis: Macular amyloidosis associated with MEN2A.

Treatment: Potent topical steroid, emollient, and keratolytic. Total thyroidectomy and left adrenalectomy shortly after the diagnosis of MEN2A.

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Discussion:

Amyloidosis is characterized by abnormal extracellular deposition of fibrillar proteinaceous substance known as amyloid. Primary cutaneous amyloidosis, a category of organ-limited amyloidosis, consists of macular, lichen, biphasic, dyschromic, and nodular forms.[1] In nodular amyloidosis, the amyloid deposits are derived from immunoglobulin light chains, similar to primary systemic amyloidosis observed in plasma cell dyscrasias. By contrast, the amyloid of macular, lichen, or biphasic amyloidosis reacts to anti-cytokeratin antibody[2], suggesting its derivation from keratinocytes and the role of chronic friction in the pathogenesis. Macular amyloidosis is clinically seen as chronic, small, confluent, brownish macules, which are often pruritic and arranged in rippled pattern. It commonly involves the upper back and extensor surfaces of extremities. Clinically, it is thought to be in the same disease spectrum as lichen amyloidosis[1]. When both forms coexist, they may be called “biphasic” amyloidosis.

The amyloid deposits in macular amyloidosis are shown as small, amorphous globules confined to the papillary dermis. Pigmentary incontinence with melanophages is also found.

Associations between macular and/or lichen amyloidosis and autoimmune diseases, including scleroderma, dermatomyositis, SLE, and primary biliary sclerosis have been noted. Rare familial forms of macular and/or lichen amyloidosis have also been reported in association with pachyonychia congenita, dyskeratosis congenita, familial palmoplantar keratoderma, and multiple endocrine neoplasia type 2A (MEN2A).[3]

MEN2A is a syndrome comprising at least 2 of the following 3 endocrine disorders: medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism (from either hyperplasia or adenoma), with MTC being the most common. Although there are some sporadic cases, MEN2A is an autosomal dominant disease, with mutation in the RET proto-oncogene.

Macular/lichen amyloidosis is common in MEN2A patients, found in 30 to 73 percent.[4-7] It is noteworthy that all MEN2A cases with macular/lichen amyloidosis, as well as the family presented here, have mutation in the codon 634 of RET proto-oncogene.[5, 8-10] The cutaneous amyloidosis may appear either before or after the diagnosis of MEN2A.[7, 11] However, it is still controversial whether to screen for MEN2A in all familial primary cutaneous amyloidosis

cases. Some investigators observed different dermatologic features between cutaneous amyloidosis associated with MEN2A (confined to upper back) and familial primary cutaneous amyloidosis (more widespread). They failed to identify the genetic association between the two entities.[9, 12]

Once MEN2A is diagnosed in an individual, relevant specific RET proto-oncogene mutation should be tested for in all family members at risk. As there have been reports of local metastatic MTC in children, thyroidectomy should be performed before the age of 6 years in all individuals with mutation in some of the specific codons, including codon 634 mentioned earlier.[13] In other words, all MEN2A cases with cutaneous amyloidosis will finally have MTC, and therefore must undergo thyroidectomy soon after the diagnosis.

Treatment of macular amyloidosis should be aimed at minimizing trauma and relieving pruritus. Current treatment options include potent topical steroids, topical calcineurin inhibitors, topical capsaicin, intralesional steroids, phototherapy, laser therapy, dermabrasion, systemic retinoids or immunosuppressive agents, among others. None of them is curative or uniformly effective.[1, 2, 14]

References

1. Black MM, Upjohn E , Albert S. Amyloidosis. In: J. L. Bolognia, J. L. Jorizzo and R. P. Rapini editors. Dermatology. London; New York: Mosby; 2008.
2. Breathnach SM. Amyloid and the amyloidoses of the skin. In: D. A. Burns, S. M. Breathnach, N. H. Cox and C. E. M. Griffiths editors. Rook's Textbook of Dermatology. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2010.
3. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988;18:1-16.
4. Paun DL, Mohora M, Duta C , Dumitrache C. Genetic testing for multiple endocrine neoplasia type 2. Rom J Intern Med 2008;46:159-63.
5. Verga U, Fugazzola L, Cambiaghi S, Pritelli C, Alessi E, Cortelazzi D et al. Frequent association between MEN 2A and cutaneous lichen amyloidosis. Clin Endocrinol (Oxf) 2003;59:156-61.
6. Pacini F, Fugazzola L, Bevilacqua G, Viacava P, Nardini V , Martino E. Multiple endocrine neoplasia type 2A and cutaneous lichen amyloidosis: description of a new family. J Endocrinol Invest 1993;16:295-6.
7. Robinson MF, Furst EJ, Nunziata V, Brandi ML, Ferrer JP, Martins Bugalho MJ et al. Characterization of the clinical features of five families with hereditary primary cutaneous lichen amyloidosis and multiple endocrine neoplasia type 2. Henry Ford Hosp Med J 1992;40:249-52.
8. Seri M, Celli I, Betsos N, Claudiani F, Camera G , Romeo G. A Cys634Gly substitution of the RET proto-oncogene in a family with recurrence of multiple endocrine neoplasia type 2A and cutaneous lichen amyloidosis. Clin Genet 1997;51:86-90.
9. Hofstra RM, Sijmons RH, Stelwagen T, Stulp RP, Kousseff BG, Lips CJ et al. RET mutation screening in familial cutaneous lichen amyloidosis and in skin amyloidosis associated with multiple endocrine neoplasia. J Invest Dermatol 1996;107:215-8.
10. Ceccherini I, Romei C, Barone V, Pacini F, Martino E, Loviselli A et al. Identification of the Cys634-->Tyr mutation of the RET proto-oncogene in a pedigree with multiple endocrine neoplasia type 2A and localized cutaneous lichen amyloidosis. J Endocrinol Invest 1994;17:201-4.
11. Karga HJ, Karayianni MK, Linos DA, Tseleni SC, Karaiskos KD , Papapetrou PD. Germ line mutation analysis in families with multiple endocrine neoplasia type 2A or familial medullary thyroid carcinoma. Eur J Endocrinol 1998;139:410-5.
12. Lee DD, Huang JY, Wong CK, Gagel RF , Tsai SF. Genetic heterogeneity of familial primary cutaneous amyloidosis: lack of evidence for linkage with the chromosome 10 pericentromeric region in Chinese families. J Invest Dermatol 1996;107:30-3.
13. Jimenez C , Gagel RF. Neoplastic disorders affecting multiple endocrine organs. In: A. S. Fauci, E. Braunwald, D. L. Kasper, S. L. Hauser, D. L. Longo, J. L. Jameson, et al. editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 2008.
14. de Argila D, Ortiz-Romero PL, Ortiz-Frutos J, Rodriguez-Peralto JL , Iglesias L. Cutaneous macular amyloidosis associated with multiple endocrine neoplasia 2A. Clin Exp Dermatol 1996;21:313-4.