Case Report

Autosomal Dominant Familial Chronic Mucocutaneous Candidiasis Associated with Acne Rosacea

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Abstract

Introduction: Autosomal dominant chronic mucocutaneous candidiasis (CMC) without endocrinopathy (OMIM 114580) is a well-described entity. The associations recorded with this disorder to date are intercellular adhesion molecule-1 (ICAM-1) deficiency and hyper-immunoglobulin E syndrome. Clinical Picture: We report a new association in a family (mother and non-identical twin sons) where acne rosacea is a prominent feature together with CMC. In addition, antibodies to thyroid microsomal and antiparietal cell were also isolated. The autoantibodies might be associated with a current "latent" endocrinopathy in particular autoimmune thyroiditis. Treatment: The patient was treated with intermittent pulses of itraconazole for the candidiasis and doxycycline initially before being substituted with isotretinoin 6 months later for the rosacea. Outcome: The patient's candidiasis responded well and has been in remission for 3 months while his rosacea continues to improve.

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Key words: Acneiform, Fungal, Inherited

Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare disorder characterised by chronic and recurrent infections, predominantly caused by *Candida albicans* affecting the mucous membranes, nails and skin. Other species of the *Candida* genus are occasional causative agents. Infections with other bacteria and dermatophytes can also occur. The infection is usually localised and there is no tendency towards systemic dissemination.

CMC can be broadly classified into familial (inherited) or non-familial (non-inherited) forms. Familial forms are inherited as autosomal dominant or recessive [McKusick number (MN) 240300 and 606415 respectively] and are associated with or without endocrinopathy (MN 212050 and 114580 respectively).[1] Two other familial subtypes, one, an autosomal dominant form with nail candidiasis and intercellular adhesion molecule-1 (ICAM-1) deficiency (MN 607644)[2] and the other, an autosomal recessive form with hyperimmunoglobulin E (MN 243700)[3] have also been described.

We report a case of autosomal dominant familial chronic mucocutaneous candidiasis without endocrinopathy associated with acne rosacea.

Case Report

A 20-year-old male presented with a 3-year history of facial erythema with pustules and telangiectasia on both his cheeks and nose. He experienced flushing when exposed to sun and heat. He denied the use of any topical application on his face. There were no systemic symptoms. There was also no history of arthralgia or proximal myopathy.

In addition, he had had a persistent cheilitis and furred tongue since the age of 6. Medical history revealed that the patient had had dystrophic toenails as a child, which responded with complete resolution to a 3-week course of itraconazole 100 mg once a day. He denied any other areas of involvement, fever, weight loss, anorexia or fatigue.

The patient's non-identical twin brother (Fig. 1) also developed acne rosacea (Fig. 2a) and cutaneous candidiasis involving his tongue and buccal mucosa (Fig. 2b) at the age of 10, but with lesser severity. His rosacea was characterised by transient facial flushing with heat exposure, inflammatory papules on a phymatous nose, with no comedones, and chalazion. His mother had both oral mucosa (Fig. 3a) and nail candidiasis (Fig. 3b) at the age of 3, but developed acne rosacea only in her forties. Her rosacea was milder and she had only nasal telangiectasia and facial flushing with heat

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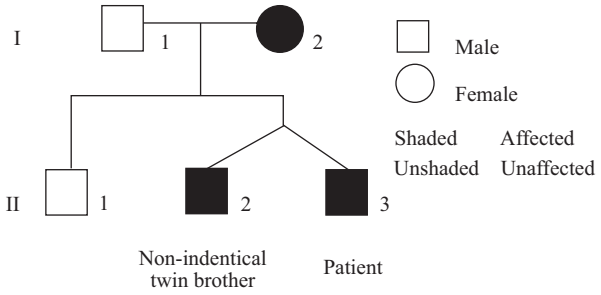

Fig. 1. Family tree illustrating an autosomal dominant inheritance.

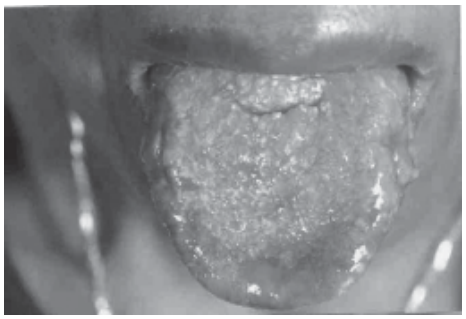

Fig. 3a.

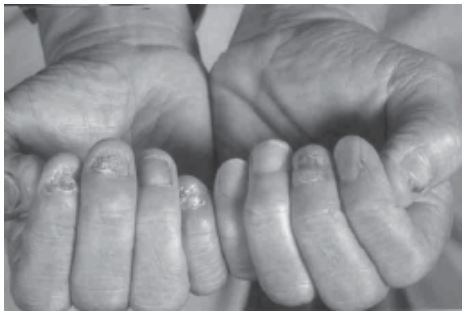

Fig. 3b.

Figs. 3a and 3b. Mucosal candidiasis involving the mucosal surface and nails in the mother.

exposure. Scrapes from buccal mucosal of his mother and non-identical twin brother showed *Candida*. Both the patient's father and elder brother were not affected. His parents were non-consanguineous. No maternal or paternal family members had similar skin findings.

On physical examination of the patient, there was perleche. Multiple whitish membranous plaques were noted on the tongue (Fig. 4a), palate and buccal mucosa. The base of the plaques was erythematous and macerated. His pharynx, conjunctivae, genitalia and scalp were unaffected. The cheek and phymatous nose had numerous papules and pustules on a background of persistent erythema and telangiectasis. The facial contours were coarse and thickened with large pores. There were no comedones seen. Ophthalmic signs included a left upper eyelid chalazion and blepharitis (Fig. 4b). The left big toe nail was dystrophic and thickened.

Fig. 2a.

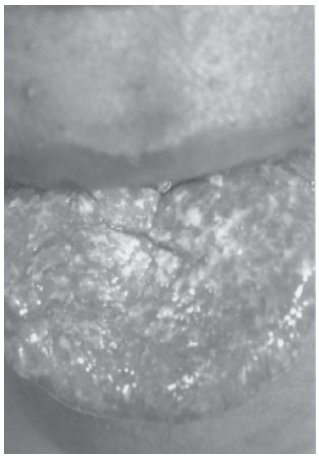

Fig. 2b.

Fig. 2a. Rosacea in the twin brother: Acneiform papules on the cheeks, bulbous coarsened nose with telangiectasia and recurrent chalazion on the left upper eyelid.

Fig. 2b. Mucosal candidiasis in the twin brother.

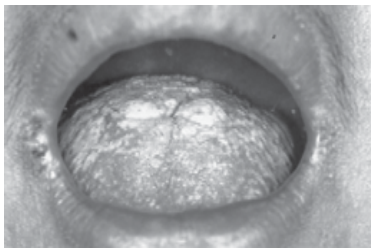

Fig. 4a.

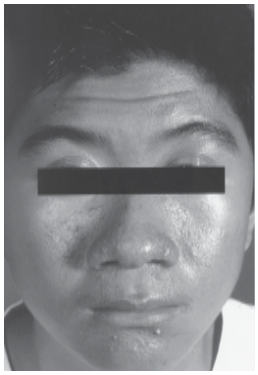

Fig. 4b.

Fig. 4a. Candidal plaques on the tongue and perleche at the angles of the mouth.

Fig. 4b. Papules and pustules on a background of erythema, telangiectasia and oedema. Note the coarsened facial features and the boggy nose. A recurrent chalazion is also seen on the left upper eyelid.

The results of the investigations on the patient are summarised in Table 1.

Despite 4 intermittent pulses of itraconazole 200 mg once a day ranging from 2 weeks to 1 month, his oral candidiasis returned within 2 to 3 weeks upon drug withdrawal. His nails, teeth and genitalia remain unaffected by candidiasis. Currently, his candidiasis has remained in clinical and mycological remission for 3 months and he is not on itraconazole.

Topical metronidazole and oral doxycycline 100 mg twice a day for 6 months was given with minimal improvement in the rosacea and this was substituted with isotretinoin 30 mg once daily. At review 2 months later, his

Table 1. Summary of Investigations and Results

Basic screen		
Full blood count, liver function test, fasting glucose, erythrocyte sedimentation rate, vitamin B12 and reticulocyte count		All normal
Iron		7.00 (9.50-30 umol/L)
Total iron binding capacity		92.00 (44-73 umol/L)
Peripheral blood film		Red blood cells were hypochromic and microcytic. 0.66%
Chest X-ray		Normal, no evidence on thyoma
Scrape	Face	Normal
	Tongue	Budding yeast cells with pseudohyphae
	Big toe nail	Normal
Culture	Tongue	*Candida albicans*
	Big toe nail	T metagrophytes var intergital No *Candida albicans*
Biopsy right face		The histology showed a widened hair follicle filled with neutrophils. There was a surrounding infiltrate of lymphocytes, histocytes and neutrophils. The lower dermis had collection of histocytes, giant cells, and macrophages around a focus of necrosis. Collections of lymphocytes were present. Periodic acid-Schiff stain was negative for fungal elements. This is consistent with acne rosacea.
Immunodeficiency screen Immunoglobulins, complements, serum electrophoresis and human immunodeficiency virus testing		Normal
Endocrine screen		
Thyroid function test, follicle-stimulating hormone, luteinising hormone, prolactin, testosterone, parathyroid-stimulating hormone, calcium, phosphate, magnesium and short synacthen test		Normal
Autoantibody screen		
Smooth muscle, mitochondrial, thyroglobulin and antinuclear antibodies		Negative
Thyroid microsomal antibody		Positive
Antiparietal cell antibody		Positive

rosacea had improved and a further 4 months of treatment was intended.

Discussion

Familial CMC, autosomal dominant, without endocrinopathy (OMIM 114580) is distinguished from other forms by dominant inheritance, the lack of associated endocrinopathy and by the lack of thyroid disease.[4,5]

Our patient illustrates the vertical transmission of a form of CMC affecting oral and buccal mucosa associated with acne rosacea. A review of the family tree indicates typical features of dominant inheritance. The non-identical twin brothers manifested the same disease, CMC and acne rosacea, at different times and degrees of severity. This variable expression is typical of autosomal dominant trait. The mother also developed severe CMC with muco-cutaneous, nails and vaginal involvement. However, her acne rosacea remains mild. Without any strong family history of the disease, it is most likely that her manifestation is due to sporadic mutation in one member of a pair of autosomal genes.

CMC patients can have antibodies targeting endocrine glands. These are found more commonly in those with an endocrinopathy (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, APECD).[6] The main immunological findings of APECD include high levels of serum antibodies reacting specifically with components of the affected organs (e.g., adrenal cortex, parathyroid glands, thyroid glands, pancreas, liver, etc).[7] In CMC patients without any endocrinopathy, antibodies to gliadin,[8] erythrocytes[9] and melanocytes[10] have been isolated. No endocrinopathies were found in our case but autoantibodies to thyroid microsomal and antiparietal cell were positive. Autoantibodies to thyroid microsomal and antiparietal cell have not been described in CMC patients without any endocrinopathy. Its relevance here remains a mystery. However, the autoantibodies might be associated with a current "latent" endocrinopathy in particular autoimmune

thyroiditis. Cell-mediated immunological testing, chemotaxis studies (polymorphonuclear leukocytes and monocytes) and *Candida* antibodies were not performed in our case. The usefulness of these test remains debatable as the diagnosis can be reached clinically and treatment regimens remains unchanged. Humoral immune studies (immunoglobulin profile, complement 3 and 4) did not reveal any abnormalities. HIV antibody test was negative. We feel that it is important to screen for HIV in adults with oral thrush who do not have diabetes and are not on corticosteroids.

Another recognised feature of CMC, present in this patient, is the reduction of iron stores resulting in overt or latent iron-deficiency anaemia. Studies have shown an impairment of iron absorption in CMC. His glossitis and angular chelitis can be associated with both CMC and low iron stores.[11] This finding can be of importance in the pathology of CMC, since chronic lack of tissue iron can result in defective epithelia formation. However, the clinical improvement after the use of iron therapy only proved to be temporary.[12]

To the best of our knowledge, there are no reports to suggest any other dermatological condition coexisting with CMC to date. Like CMC, the expression of rosacea is variable, with a more severe affliction in our patient compared to his brother. The mechanism of association between CMC and acne rosacea is not understood. Although the pathogenesis of rosacea remains speculative, patients with rosacea are not known to be associated with any immune disturbance.[13]

Conclusion

In conclusion, acne rosacea and parietal cells and thyroid autoantibodies can be further included as features of familial CMC, autosomal dominant (without any clinical endocrinopathies) (OMIM 114580).

REFERENCES

1. Coleman R, Hay RJ. Chronic mucocutaneous candidiasis associated with hypothyroidism: a distinct syndrome? Br J Dermatol 1997;136: 24-9.
2. Zuccarello D, Salpietro DC, Gangemi S, Toscano V, Merlino MV, Briuglia S, et al. Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis. J Med Genet 2002;39:671-5.
3. Dreskin SC, Goldsmith PK, Gallin JI. Immunoglobulins in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome: deficiency of anti-*Staphylococcus aureus* immunoglobulin A. J Clin Invest 1985;75:26-34.
4. Loeys BL, Van Coster RN, Defreyne LR, Leroy JG. Fungal intracranial aneurysm in a child with familial chronic mucocutaneous candidiasis. Eur J Pediatr 1999,158:650-2.
5. Sams WM. Jr, Jorizzo JL, Snyderman R, Jegasothy BV, Ward FE, Weiner M, et al. Chronic mucocutaneous candidiasis: immunologic studies of three generations of a single family. Am J Med 1979;67:948-59.
6. Edwards JE Jr, Lehrer RI, Stiehm ER, Fischer TJ, Young LS. Severe candidal infections: clinical perspective, immune defense mechanisms, and current concepts of therapy. Ann Intern Med 1978;89:91-106.
7. Peterson P, Pitkanen J, Sillanpaa N, Krohn K. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): a model disease to study molecular aspects of endocrine autoimmunity. Clin Exp Immunol 2004;135:348-57.
8. Garcia YH, Diez SG, Aizpun LT, Oliva NP. Antigliadin antibodies associated with chronic mucocutaneous candidiasis. Pediatr Dermatol 2002;19:415-8.
9. Oyefara BI, Kim HC, Danziger RN, Carroll M, Greene JM, Douglas SD. Autoimmune hemolytic anemia in chronic mucocutaneous candidiasis. Clin Diagn Lab Immunol 1994;1:38-43.
10. Howanitz N, Nordlund JL, Lerner AB, Bystryn JC. Antibodies to melanocytes. Occurrence in patients with vitiligo and chronic mucocutaneous candidiasis. Arch Dermatol 1981;117:705-8.
11. Higgs JM, Smith P, Smith T. Measurement of 59Fe absorption and retention in patients with familial chronic muco-cutaneous candidiasis using the method of whole body counting. Clin Exp Dermatol 1976;1: 369-76.
12. Higgs JM. Chronic mucocutaneous candidiasis: iron deficiency and the effects of iron therapy. Proc R Soc Med 1973;66:802-4.
13. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol 2004;51:327-41.