

Discoid lupus erythematosus-like lesions and stomatitis in female carriers of X-linked chronic granulomatous disease

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SUMMARY

The skin and oral mucosa were studied in an unselected series of carriers of X-linked chronic granulomatous disease, a hereditary condition in which phagocytic cells display a pronounced functional defect.

Three carriers had discoid lupus erythematosus (DLE)-like skin lesions which histopathologically were consistent with DLE of the hypertrophic and profundus type. Four patients had experienced photosensitivity in childhood. Seven patients had recurrent aphthous-like stomatitis which should be distinguished from the recurrent aphthous stomatitis seen in otherwise healthy individuals.

The remarkably high incidence of DLE-like symptoms in heterozygous carriers might be related to the presence of mixed populations of defective and normal phagocytes. The variable expression of skin symptoms may be related to uneven distribution of abnormal to normal phagocytes.

Female patients with these clinical symptoms, especially the combination of DLE-like skin lesions and aphthous-like stomatitis, should be suspected of being carriers of chronic granulomatous disease and studies of phagocyte function *in vitro* should be performed, since the diagnosis of the carrier state is of utmost importance for genetic counselling before pregnancy.

Chronic granulomatous disease (CGD) is a hereditary condition in which polymorphonuclear leukocytes (PMN) display a pronounced bactericidal defect (Quie, 1975) caused by a derangement in the normal oxidative metabolism of these cells. Most reported cases have involved boys (Johnston & Newmann, 1977) in whom the disease is inherited as an X-linked recessive trait (Windhorst *et al.*, 1968; Quie, 1975). Affected children suffer from severe recurrent and chronic infections caused by

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catalase-positive bacteria and fungi (Johnston & Newmann, 1977). Skin infections, eczematous reactions (Windhorst & Good, 1971), suppurative lymphadenitis, otitis and stomatitis (Wysocki & Brooke, 1978) may be seen in early life, and very often more severe infections like pneumonia, osteomyelitis, abdominal abscesses, meningitis and septicaemia may occur.

PMN from the heterozygous female carriers of the X-linked form display a partial defect in oxidative metabolism and bacterial killing (Windhorst *et al.*, 1968). Studies of the ability of individual PMN from CGD homozygotes and heterozygotes to reduce nitroblue tetrazolium (NBT), a function of normal oxidative metabolism, reveal mixed populations of normal and defective cells (Windhorst *et al.*, 1968). This finding is in agreement with the Lyon hypothesis of random X-chromosome inactivation (Lyon, 1962). However, most carriers are free of undue infections, but skin diseases including discoid lupus erythematosus (DLE) (Landing & Shirkey, 1957; Douglas, Davis & Fudenberg, 1969; Klebanoff & White, 1969; Thompson & Soothill, 1970; Schaller, 1972; Humbert *et al.*, 1976) and Jessner's lymphocytic infiltration of the skin (MacFarlane, Speirs & Sommerville, 1967; Nelson, Dahl & Goltz, 1977) have been reported. Recurrent aphthous stomatitis has also been reported in these carriers (Windhorst *et al.*, 1968; Douglas, Davis & Fudenberg, 1969; Schaller, 1972).

In order to describe in greater detail the clinicopathological findings and their frequency of expression in the skin and oral mucosa, we have undertaken a prospective study of nine unselected known carriers of X-linked CGD.

MATERIAL AND METHODS

Eight mothers, one sister and a maternal aunt of boys with CGD, representing all who could be contacted through the Danish registry for immunodeficiencies, were studied.

The carrier state was established by functional tests on peripheral blood PMN *in vitro*, showing decreased intracellular killing of *Staph. aureus* (Koch, Sogaard & Christensen, 1973) and decreased stimulated oxidative metabolism as judged by hexose monophosphate shunt activity, chemiluminescence, and reduction of NBT by standard techniques. By all parameters the carriers demonstrated a partial defect, resulting in intermediate values between those of affected boys and normal controls.

In three cases punch biopsies were taken from skin lesions for histopathological examination, and in two cases direct immunofluorescence study was performed with fluorescein isothiocyanate-conjugated anti-human IgG, IgA, IgM, anti-fibrinogen and complement C₃. In two cases biopsies taken previously were reviewed.

The oral mucosa was examined clinically, histopathologically and immunopathologically during attacks of stomatitis in four patients (case 1-3 and 5) and clinically in two patients (case 4 and 9). Biopsies from affected as well as unaffected oral mucosa were divided, one half being processed for routine microscopy, the other half processed for direct immunofluorescence (IF) studies according to a method described previously (Schjødt *et al.*, 1974) with antisera for the presence of fibrinogen, IgG, IgA, IgM and complement C₃.

CASE REPORTS

Case 1

A.J., 42-year-old woman with a healthy daughter and a son with CGD. The patient had from the age of 7 years suffered from recurrent aphthous-like stomatitis with intervals of weeks or a few months. From 36 years of age recurrent hidradenitis in the axillae and genitofemoral region was present, and a sterile abscess in the buttock had been drained. From 30 years of age infiltrated, bluish red, slightly scaling small plaques had been present on the dorsa of the hands (Fig. 1), in the sternal region and periodically on the cheeks and nose. Following some previous lesions, slightly depressed



FIGURE 1. Case 1. Infiltrated plaques on the hands.

hypopigmented scars were seen. On the tips of the toes deep-set, partly haemorrhagic vesicles were seen. During treatment with hydroxychloroquine (Ercoquin) 250 mg twice a day the skin changes almost cleared, the stomatitis decreased in intensity and the condition is now controlled on 250 mg daily. Skin biopsies had been taken 1 year and 5 years before treatment.

Case 2

E.L.O., 36-year-old mother to a boy with CGD. The patient had suffered from photodermatitis in the summer since early childhood, but the photosensitivity has decreased in adult life. From 14 years of age recurrent aphthous-like stomatitis had been present at intervals of weeks or a few months. From the age of 24 recurrent eruptions of red, infiltrated lesions on the chin, cheeks, and forehead had been present, often with rosacea-like papules (Fig. 2). On both palms dark red, well demarcated nummular lesions were seen (Fig. 3). On the tips of some fingers and toes deep-set vesicles and slight scaling were present. During treatment with hydroxychloroquine (Ercoquin) 250 mg twice a day the skin changes almost cleared, and the stomatitis decreased in severity after 1 month. The condition is controlled on 250 mg daily. One skin biopsy was taken before treatment.

Case 3

E.F.C., 28-year-old woman, sister to two boys who died from CGD. Another sister (case 6) had a son with CGD. The patient had from the age of 7 years suffered from recurrent stomatitis at intervals of weeks. From 14 years of age red, infiltrated, slightly scaling lesions were seen on the hands and fingers and periodically over the shoulders. Typical perniosis of fingers and toes was present. Deep-set haemorrhagic vesicles and slight scaling were seen on the tips of the big toes. A skin biopsy had been taken 5 years previously and new biopsies were taken.

Case 4

P.S.J., 32-year-old mother to a boy with CGD. The patient suffered in childhood from polymorphous light eruption during spring and summer. She was examined at the Finsen Institute at the age of

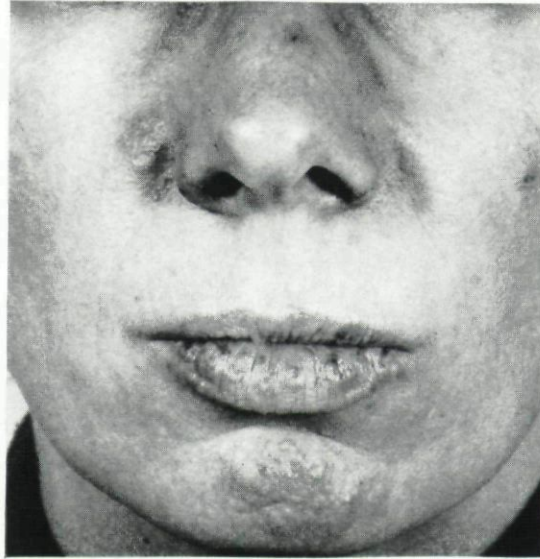


FIGURE 2. Case 2. Bluish-red rosacea-like infiltrates on the face.



FIGURE 3. Case 2. Well-demarcated dark red patch on right palm.

7 years, when she presented with photodermatitis of the cheeks. At the present examination the light sensitivity had decreased, and the skin is now normal except for slight comedo acne. For many years the patient has suffered from recurrent stomatitis about once a month.

Cases 5-9

The findings in these cases are summarized in Table 1. One of these mothers mentioned photo-dermatitis in childhood and three suffered from recurrent aphthous-like stomatitis. Three patients had been seen by dermatologists because of hand eczema classified as irritant eczema. One patient had acute glomerulonephritis with a typical course at the age of 11 years, but no sequelae. One patient had been treated for sterile subcutaneous abscesses in the breast.

TABLE 1. Clinico-pathological findings in female carriers of CGD

Case		Age yr	Photo-sensitiv-ity	DLE-like skin changes	LE serol-ogy	Recurrent stoma-titis	Abscesses Hidrade-nitis	Hand eczema	Associated findings
1	AJ	42		+(30)	neg	+(7)	+(36)		
2	ELO	36	+(1)	+(24)	neg	+(4)	+		Sequelae of chorio-retinitis in right eye
3	EFC	29	+(14)	+(14)	neg	+(7)			
4	PSJ	32	+(EC)		neg	+(C)			
5	JRJ	38	+(C)		neg	+(23)	+	+	Acute glom.neph. (11). No seqv.
6	TFN	25			NT	+(C)			
7	BR	42			NT			+	
8	KL	27			NT				
9	JBL	45			NT	+		+	

NT = not tested; () = estimated age at onset; EC = early childhood; C = childhood.

RESULTS

Laboratory findings

In all cases the heterozygous carrier state was established by granulocyte function tests as mentioned previously. In five cases tested no antinuclear antibodies, anti-DNA-antibodies or LE cells were found, and the Latex fixation test was normal. The blood tests did not disclose involvement of other organs.

Histopathological findings in the skin

The changes seen in the seven biopsies are summarized in Table 2 and some features illustrated in Figs 4-5. Dermal perivascular and perifollicular lymphocytic infiltration, though minor in one biopsy (case 3), and telangiectasia were found in all biopsies. Quite considerable hyperkeratosis associated with acanthosis, parakeratotic plugging and fibrosis of the papillary layer were found in four biopsies, including one biopsy from each of the three cases.

Immunopathologically (case 1) minimal granular deposits of IgM and more marked deposits of complement C₃ were found at the basement membrane area of affected skin. In the upper part of the dermis considerable deposits of fibrinogen were found. In case 2 no deposits of immunoglobulins, complement C₃ or fibrinogen were found in a biopsy from affected skin of the hand.

Oral findings

Seven of the nine carriers gave a history of recurrent ulceration of the oral mucosa (Table 1). The number of recurrences varied from once a year to once a fortnight and varied in individuals as well. The duration of the ulcers ranged from 4-14 days with an average of 7 days.

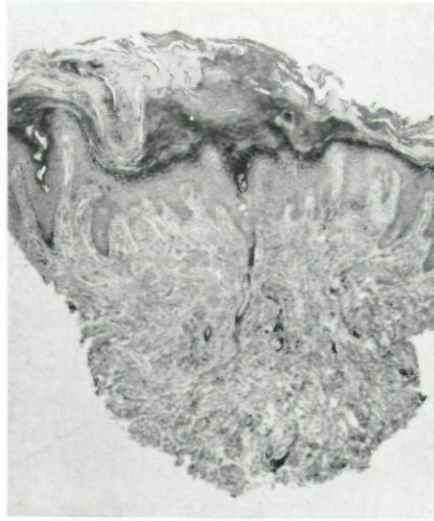


FIGURE 4. Hyperparakeratosis with plugging, irregular acanthosis, telangiectasia of papillary layer, slight lymphocytic infiltration (HE \times 32).

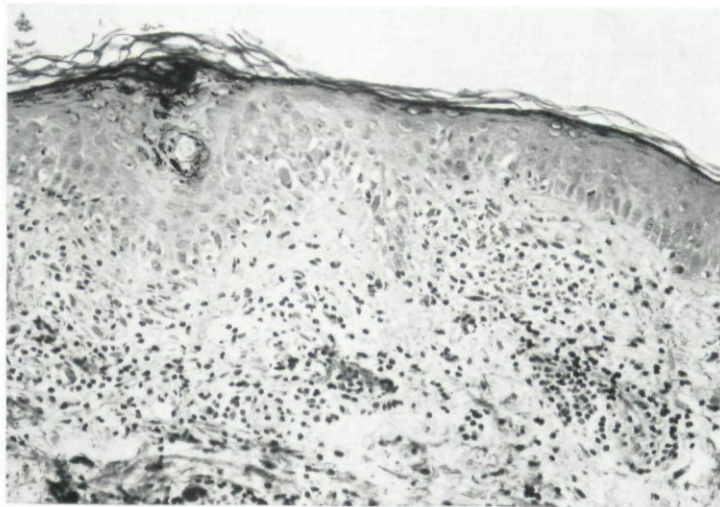


FIGURE 5. Liquefaction degeneration of basal layer with Civatte bodies (HE \times 225).

Clinically the five cases (cases 1-5) examined during the active stage showed aphthous-like ulcers located on buccal and labial mucosa (5), gingiva (5), tongue (3), floor of mouth (1) and palate (1) (Figs 6-7). The ulcers had a size of 1-20 mm with the smaller ones dominating (Fig. 6) and were surrounded by a zone of erythema with a width ranging from 0-10 mm. In three cases the ulcers were associated with white areas which were most prominent during the healing stage (Fig. 7). The white changes faded in the course of a few weeks, but were permanent in some areas in one case.

Histopathologically ulceration of the epithelium was found and the connective tissue was infiltrated

TABLE 2. Histopathological findings in affected skin of female carriers of CGD

Case no.	1			2		3	
Biopsy no.	1	2A	2B		1A	1B	2
Scale crust					+		
Plugs	+		+	+			+
Hyperkeratosis	+		+	+	+		+
Acanthosis	+		+	+	+		
Epidermal atrophy		+		+	+		
Liquefaction degeneration of basal layer		+	+	+	+		
Thickened basal membrane				+			
Epidermal lymphocytes	+	+	+	+	+		
Epidermal lymphocytes and vesicles				+	+		
Dermal lymphocytes	+	+	+	+	+	+	+
Subcutaneous lymphocytes	NS	+	+	NS	NS	NS	NS
Oedema of papillary layer		+	+	+		+	+
Fibrosis of papillary layer	+	+	+	+			+
Telangiectasia	+	+	+	+	+	+	+

NS: No subcutaneous tissue in the biopsy.

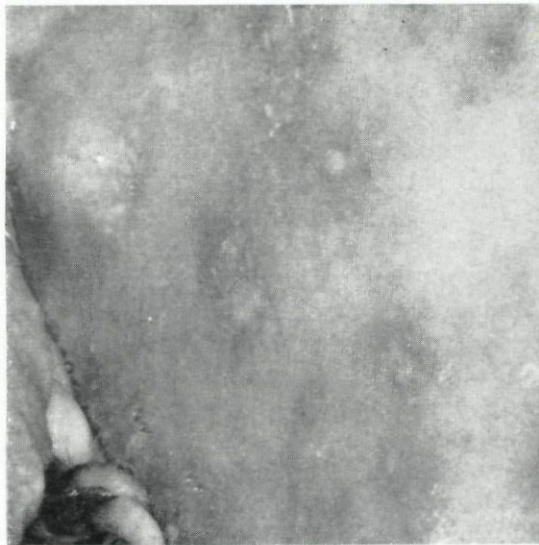


FIGURE 6. Case 3. Multiple small ulcers on left buccal mucosa in carrier for CGD. Note similarity to recurrent aphthous stomatitis of herpetiform type.

by inflammatory cells, predominantly lymphocytes. Corresponding to the white areas mentioned previously the epithelium showed slight to moderate hyperparakeratosis and acanthosis, and a diffuse inflammatory infiltrate, dominated by lymphocytes, was seen in the connective tissue. Epithelioid cell granulomas were not found.



FIGURE 7. Case 5. Ulcers on left buccal mucosa (arrows) in carrier for CGD. Note white area in relation to ulcers and broad zone of erythema (triangle).

Immunopathologically the oral lesions showed deposits of fibrinogen at the basement membrane area in all four cases examined and granular deposits of complement C_3 in two cases. Deposits of immunoglobulins were not demonstrated. IF staining of clinically normal oral mucosa was negative.

DISCUSSION

Most previous reports contain only brief reference to skin diseases in female carriers of CGD, but a few more detailed case reports have been published (Schaller, 1972; Humbert *et al.*, 1976; Nelson, Dal & Goltz, 1977). Three cases (Schaller, 1972, Humbert *et al.*, 1976) had LE-like lesions predominantly of the hands and the face, like our patients. One carrier (Schaller, 1972) also had Raynaud's phenomenon, episodes of arthralgia, pleurisy, stomatitis, and unexplained fever, but a diagnosis of systemic LE was not definitely established. Our series was unselected and showed a remarkably high frequency of skin symptoms.

The photosensitivity, though decreasing with age, the cutaneous manifestations and their response to antimalarials in our patients are in many respects consistent with DLE. The skin changes on fingers and toes are similar to chilblain LE (Millard & Rowell, 1978). The deeper rosacea-like infiltrates on the face and the sterile, subcutaneous abscesses have features in common with LE profundus (Eickstedt & Hassenpflug, 1962). Histopathologically the findings ranged from almost pure lymphocytic infiltration of the Jessner type to lesions consistent with LE, and biopsies with changes similar to chronic dermatitis. Since these lesions are clinically of the same type and do occur with a variable histology in the same patient we find it reasonable to interpret our findings as a pleomorphic type of DLE. The slight lymphocytic infiltration between fat cells in the two biopsies in which subcutaneous tissue was present and hypertrophic changes in other biopsies are consistent with LE-hypertrophicus et profundus (Bechet, 1942; Eickstedt & Hasselpflug, 1962; Dammert, 1971; Otani, 1977). Pigmented histiocytes of the type described by Symchych, Wanstrup & Andersen (1968) in children with CGD were not found.

The stomatitis reported previously in CGD carriers has been interpreted as recurrent aphthous stomatitis (RAS) (Windhorst *et al.*, 1968; Douglas *et al.*, 1969). The recurrent ulcerative stomatitis in our study is comparable with RAS with regard to time of onset, number of recurrences and duration of attacks. Furthermore the ulcers bear an apparent similarity to RAS. However, differences exist: 1. The erythematous halo is of varying width and more extensive than usually seen in RAS. 2. White areas are seen in relation to the ulcers, which histologically show hyperparakeratosis. 3. The ulcers occurred on the attached gingiva in all cases, whereas RAS only rarely affects the gingiva. 4. The IF examination did not reveal deposits of immunoglobulins in contrast to what is found in RAS (Donatsky & Dabelsteen, 1977). It seems, therefore, justified to distinguish between the recurrent stomatitis seen in CGD carriers and RAS.

One of our patients had acute glomerulonephritis in childhood and another patient sequelae after chorioretinitis. Other diseases with an immunological pathogenesis have been reported in carriers of CGD—rheumatic fever and rheumatic heart diseases (Macfarlane, Speirs & Sommerville, 1967; Windhorst *et al.*, 1968), ulcerative colitis (Windhorst *et al.*, 1968) and polyarthritis (Thompson & Soothill, 1970; Schaller, 1972).

Humbert *et al.* (1976) investigated nineteen female LE patients (11 DLE, 8 SLE) for the presence of laboratory findings characteristic of the carrier state for CGD, but none of these patients turned out to have this abnormality. In future screening for this defect among female LE patients it might be beneficial to select a subgroup with recurrent stomatitis, as this symptom seems to be common in the carrier state as shown in our study.

LE has not been reported in patients with CGD. This may be because of the rarity of LE in males or because most boys with CGD have not yet reached adulthood. Since the prognosis is steadily improving on correct diagnosis and treatment it should be important to look for similar skin and mucous membrane symptoms in boys with CGD.

As shown in our study the clinical manifestations in CGD carriers vary considerably in severity and extent. Evidence of uneven distribution of abnormal to normal PMN in carriers has been presented (Biggar, Buron & Holmes, 1976; Repine *et al.*, 1975), and Thompson & Soothill (1970) suggested a correlation between the individual capacity for NBT reduction and the presence of LE-like symptoms. Also, varied involvement of the monocyte-macrophage cell line may be inferred as a pathogenetic factor (Rodey *et al.*, 1969; Lehrer, 1975).

There is no straightforward explanation for the remarkably high incidence of skin symptoms in carriers of X-linked CGD. The stomatitis might result from impaired local defence against oral microorganisms. Stomatitis is thus a frequent finding in affected homozygous boys (Johnston & Newman, 1977). The characteristic skin symptoms are, however, not common in CGD. It may be speculated that a defect in the 'scavenger function' of phagocytes might lead to delayed, or inappropriate elimination of infectious agents, damaged cells and tissue components. This could lead to persistence of antigenic material or to delayed inactivation of biologically active factors. The presence of LE-like lesions in heterozygotes and the absence of these signs in homozygotes might thus be related to the presence in heterozygotes, of both defective and normal phagocytes, the latter being able to respond normally to an abnormal inflammatory stimulus.

The diagnosis of the carrier state of X-linked CGD is of utmost importance for genetic counselling before pregnancy. Not only is it possible to determine the sex of the fetus by amniocentesis, but it is also possible to diagnose CGD prenatally in a male fetus using blood obtained by fetoscope from placental vessels (Newburger *et al.*, 1979). Quite recently (Fikrig *et al.*, 1980) decreased capacity for NBT reduction of skin fibroblasts from CGD patients and carriers, compared to normal skin fibroblasts and cultured amniotic fibroblasts, has been reported. This offers a possibility of prenatal diagnosis of CGD without the hazards of puncture of placental vessels. The novel finding of reduced

capacity for NBT reduction in skin fibroblasts may also be pertinent to the skin symptoms in carriers of CGD.

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