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Dermatomyositis-like Syndrome in X-linked Hypogammaglobulinemia

Case-report and Review of the Literature

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A case of dermatomyositis-like syndrome is described in a 19-year-old man with a history of Bruton's hypogammaglobulinemia. Although the patient had central-nervous-system manifestations (seizures), no echovirus was isolated in the cerebrospinal fluid, in contrast to previously reported cases. Data for our case and the 15 cases previously reported in the literature are reviewed. HLA typing of our patient revealed the presence of HLA B8 and DR3, which seems to play a major role in juvenile dermatomyositis.

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Congenital agammaglobulinemia, also referred to as hypogammaglobulinemia or Bruton's disease, is the most common immunologic deficiency syndrome. The disease is transmitted by a recessive, X-linked trait. In 1956, Janeway et al. (1) reported a cutaneous and muscular syndrome resembling dermatomyositis, and often termed dermatomyositis-like syndrome, in patients with congenital agammaglobulinemia (2, 3). This lethal syndrome is often accompanied by central-nervous-system manifestations, with persistent infection by an echovirus. The involvement of echovirus in the onset of the cutaneous and muscular manifestations has therefore been suggested (4, 5). We describe here a case of dermatomyositis-like syndrome in which no echovirus could be isolated. No previous reports on this disorder were found in dermatological journals, and this prompted us to publish our case report.

CASE REPORT

A 19-year-old man with a history of Bruton's hypogammaglobulinemia was hospitalized in February 1983. The family history was negative. The disease course began when the patient was 6 months old, with postvaccinal poliomyelitis (Sabin live oral poliovirus) leaving amyotrophy of the upper limbs and the right leg. At one year of age, an episode of myocarditis was followed by recurrent otitis and upper respiratory tract infections. Hypogammaglobulinemia was diagnosed and intramuscular gammaglobulin treatment was begun, but the doses were low and the treatment was given irregularly. In 1979, the patient suffered from prolonged diarrhea and developed thrombopenia in January 1982. A bone marrow biopsy revealed lymphoid hyperplasia and diffuse myelofibrosis.

On admission in 1983, a global hypotrophy with amyotrophy, chronic purulent sinusitis and skin manifestations were noted. The cheeks were covered by a symmetrical erythema (butterfly pattern) (Fig. 1). There was also maculo-papular exanthema over the extensor surfaces of the arms and the forearms (Fig. 2), and over the dorsal surfaces of the proximal interphalangeal and metacarpophalangeal joints (Fig. 3). These cutaneous manifestations began in 1981 when the patient was 16 years old and remained stable.

Biological tests revealed anemia (103 g/l) with microcytosis, thrombopenia (47 giga/l), hypogammaglobulinemia (< 0.5 g/l) reflecting the insufficiency of the replacement therapy. Other laboratory values were transaminases SGOT 26 IU/l (normal < 20 IU/l), SGPT 16 IU/l (normal < 20 IU/l), LDH 358 IU/l (normal < 255 IU/l), aldolase 4.25 IU/l (normal < 4 IU/l), gamma GT 91 IU/l (normal < 25 IU/l), alkaline phosphatases 653 IU/l (normal < 225/l). Liver biopsy disclosed non-specific lesions. Bone marrow biopsy revealed exacerbated myelofibrosis, with infiltration of T8-positive lymphoid cells. Typing of the lymphocyte subpopulations confirmed the absence of circulating B lymphocytes (31% T4, 50% T8) and HLA typing revealed the presence of HLA A1, A2, B8, B4, DR3. A skin biopsy showed perivascular lymphohistiocytic infiltrates in the dermis.

The patient received 400 mg/kg of intravenous immune globulin (Sando-globulines, Sandoz Laboratories) every 3 to 4 weeks from 1983 until his final hospital admission (IgG

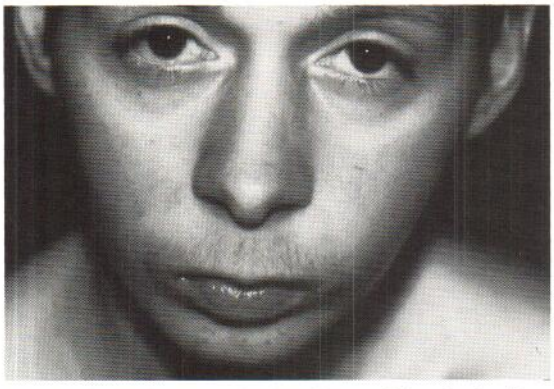

Fig. 1. Bilateral symmetrical erythema of the cheeks (butterfly pattern).

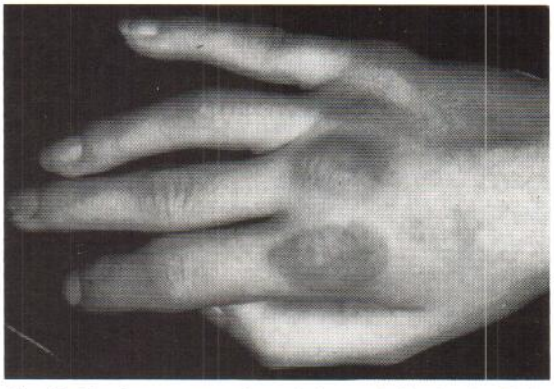

Fig. 3. Erythemato-papulous lesions of the back of the hands.

level between 6 and 8 g/l.) The thrombopenia remained stable (between 40 and 60 giga/l). In June 1984, the patient developed an acute, open angle glaucoma that required trabectulotomy after failure of medical treatment. In August 1984, abundant rectal bleeding prompted discovery of an angioma of the right colon treated by laser. In October 1984, the patient had two seizures with prolonged loss of consciousness. Electroencephalography showed a dysrhythmia with diffuse delta bursts. Discrete cerebral atrophy was seen on computed tomographic scans. The patient's general condition declined steadily during 1984, with gradually increasing muscle weakness. A biopsy of the left quadriceps muscle showed marked atrophy and an interstitial infiltrate consisting of histiocytic cells and a few lymphocytes.

The phosphorylase, lipid and glycogen contents were normal. Immunofluorescence studies revealed C3 deposits in the interstitium. Electron microscopy disclosed non-specific myofibrillar modifications (architectural disorganization, swelling of reticular canals). No viral particles were identified. The endothelial cells of the capillaries contained tubulo-reticular inclusions, usually observed in dermatomyositis. In March 1985, he developed a severe episode of congestive cardiac failure and died soon after admission. Permission for necropsy was refused.

Repeated virological investigations were made to detect viruses by cultures on continuous cell lines and on human embryonal cells as well as by inoculation into newborn mice. Tests were performed on samples from the upper aero-digestive tract, on cerebrospinal fluid (in Oct. 84 and March 85), in stools, and in urine, in the skin (Oct. 84) and the muscle biopsies. All cultures were negative.

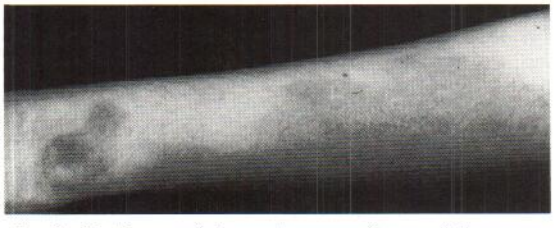

Fig. 2. Erythema of the extensor surfaces of the upper limbs.

DISCUSSION

Clinical findings in our patient faithfully reproduce the clinical picture initially described in 1956 and later termed 'dermatomyositis-like syndrome' (Table I). The skin manifestations consisted in erythema of the face (butterfly pattern) and extensor surfaces of the limbs (with marked enhancement at the level of the metacarpophalangeal and interphalangeal joints). The lesions varied from one day to the next, but their topography remained stable. Initial evaluation of muscular involvement was rather difficult because our patient had residual muscle defects after postvaccinal poliomyelitis. However, the progressive muscle weakness became severe toward to close of the disease course. The cardiac manifestations responsible for his death could also be explained by involvement of the striated muscle. Contrary to most of the other cases reported in the literature, our patient initially had no neurologic signs, but he had two seizures during the last months of the disease course. However, it should be mentioned that neurologic signs are often extremely discrete during this disease, in particular at the onset, and can even be completely absent (3).

The hypothesis usually retained for the pathogenesis of this syndrome is persistent viral infection, namely by an echovirus. In all recent cases reported in the literature, viruses were isolated often repeatedly, usually in the CSF but also occasionally in muscle. The virus was generally an echovirus, although an echovirus-adenovirus combination or an

Table I. *Hypogammaglobulinemia and dermatomyositis-like syndrome (15 literature cases plus the present report).*

Patient	Ref.	Age	Clinical features of dermatomyositis-like syndrome	Meningo-encephalitis	Viral cultures	Clinical course
1	14	Unknown	Erythema of extensor surfaces of joints; edema; muscle infiltration	Yes (no details)	Echovirus 9, adenovirus 12, (autopsy) CSF	Died
2	14	Unknown	Erythema of extensor surfaces of edema, muscle infiltration	Yes (no details)	Echovirus 9, CSF	Died
3	5	17	Erythema of eyelids and extension surfaces of the hand joints, edema, mucle induration	Seizures headache, altered mental status	Not performed	Died
4	15	5	Erythema of extensor surfaces of legs, edema, polymyositis	Confusion, loss of memory	Echovirus 24, CSF, liver urine stools, bone marrow, pleural fluid, kidney	Died
5	3	24	Cutaneous atrophy of legs, edema polymyositis	Headaches, nuchal rigidity	Echovirus 9, CSF	Died 10 wk.
6	3	15.5	Polymyositis	Deafness	Echovirus 30 & 19, CSF and stools	Died 2.5 yr.
7	3	3.5	Transient erythema of face and limbs, polymyositis	No signs	Echovirus 33, CSF	Died 7 mo.
8	16	11	Erythema of right biceps, edema, polymyositis	Headache, seizure, tremor, altered mental status	Echovirus 11, CSF	Died 29 mo.
9	6	21	Erythema of legs, edema, polymyositis	Neurologic signs 2 yr after onset of dermatomyositis (seizures, confusion)	Echovirus 3, CSF	Died 3 yr.
10	7	18	Polymyositis	No	Echovirus 17 & 3, CSF muscle	Alive 4 yr.
11	4	16	Cutaneous atrophy of legs, polymyositis	Nerve VI + VII paresis, ataxia, deafness, nystagmus	Echovirus 5, CSF, blood	Died 4 yr.
12	17	32	Edema, polymyositis	Lethargy	Echovirus 11, CSF, muscle	Alive 5.5 yr.
13	18	7	Edema, polymyositis	Seizures, deafness	Echovirus 7, liver, spleen, kidney	Died 2 yr.
14	19	29	Transient erythema of limbs, edema polymyositis	Confusion seizures	Echovirus 11, CSF, blood urine, lung, muscle	Died 1 yr.
15	20	8.5	Edema of face, cutaneous atrophy (face and lower extremities), polymyositis	Cerebral CT Scan: enlargement of scissural gyri + liquid in the subarachnoïdal space	Echovirus 13, CSF	Died 11 mo.
16	this case	16	Erythema of face and extensor surfaces of the joints, polymyositis	Seizures	(-)CSF, throat, urine, skin, blood, stools, muscle.	Died 2 yr.

association of two echoviruses have been found. However, this type of virus is also found in agammaglobulinemic patients without cutaneo-muscular signs, namely in cases of meningoencephalitis. These patients are particularly susceptible to enteroviruses, which are non-enveloped viruses (6, 7). Enteroviruses replicate without insertion of the viral protein into the host cell membrane prior to cell lysis. Defence is thus primarily dependent on antibody immobilization of the virus, as there is limited opportunity for recognition by T-cells. In our patient, no echovirus was isolated despite repeated viral cultures. This might reflect intermittent presence of the virus in the CSF or the absence of echovirus infection in our patient. An alternate hypothesis is that our patient suffered from some other virus infection.

The role of the Coxsackie-B virus has recently been suggested in adults and adolescents with dermatomyositis. This type of virus was sought in particular because the Coxsackie-B virus is known to produce myopericarditis and epidemic myalgia in humans (8). Raised Coxsackie-B virus neutralization titres have been reported in association with both dermatomyositis and polymyositis (9). However, infectious virus has not been isolated from affected muscle, whereas virus-like particles have been reported in biopsy samples from patients with polymyositis or dermatomyositis (10).

By quantitative slot-blot hybridizations using a Coxsackie-B virus-specific probe performed on skeletal muscle biopsy samples from patients with adult polymyositis and juvenile dermatomyositis, the presence of Coxsackie-B virus RNA was established in the majority of cases, whereas no viral sequences were found in the control biopsy samples (11). This investigation was not performed in our patient and no direct proof of a Coxsackie infection could be obtained. An immunogenetic mechanism seems to play a major role in juvenile dermatomyositis. An increased frequency of HLA-B8 (55% of patients) and HLA-DR3 (90%) has been reported (12, 13). Interestingly, our patient had the tissue group HLA B8 and DR3. This phenotype is found in only 5% of the European Caucasian population, and neither Bruton's disease nor dermatomyositis-like syndrome are known to be associated with any particular phenotype.

The pathogenesis of the dermatomyositis-like syndrome in patients with congenital agammaglobulinemia is still obscure. Further studies to detect Coxsackie or echovirus using specific DNA probes should be performed in these patients as soon as these techniques become widely available.

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