

Primary Macroglobulinemia Presenting as Multiple Ulcers of the Legs

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Abstract. Multiple ulcers developed on the lower legs of a 67-year-old man suffering from macroglobulinemia. Histological and direct immunofluorescence studies on biopsy specimens taken from the lesions revealed dilation of capillaries, deposition of large quantities of IgM in the vessels, and deposition of C3 in the vessel walls. A marked increase in blood Clq binding immune complexes was also noted. These findings suggest immune complex-induced ulceration. The fact that IgM-type cryoglobulins were positive implies that cryoglobulins derived from macroglobulins may play an important causative role in ulceration.

Key words: Macroglobulinemia; Multiple ulcers; Immune complex disease; Cryoglobulins

Macroglobulinemia was first reported by Waldenström in 1944 (1). While this disease seemed to resemble multiple myeloma, in view of the principal symptoms hyperglobulinemia and swelling of lymph nodes, he suggested it to be a new syndrome differing from multiple myeloma in that the increased cells in blood, bone and bone marrow lymphoid. In 1948, this disease was named as Macroglobulinemia Walderström, and accepted as a new entity (2). In Japan, macroglobulinemia, especially the primary type, had been considered to be a relatively rare disease even in the field of internal medicine (3). In recent years, however, with the advances made in testing methods, the frequency of this disease has gradually increased. On the other hand, in the dermatological field, the skin eruption peculiar to this disease has seldom been observed, and there have also been few reports on the occurrence of non-specific skin eruption.

We present here a case of macroglobulinemia in which multiple ulcers developed on the lower legs, with a remarkable increase in immunoglobulins and deposition of IgM and C3 in the vessels.

REPORT OF A CASE

The patient was a 67-year-old man, who was first seen at our dermatology clinic on October 11, 1979 with a complaint of ulcers on his lower legs. He suffered from a right hip joint fracture due to a traffic accident about 20 years previously; he has had hypertension for about 10 years. At the age of 65 years he underwent a surgical operation on a right inguinal hernia. There was no specific family history.

Since 1977, both of his lower legs had become edematous every cold season, when the edema had been relieved each time by oral administration of a diuretic. In the summer of 1978, he noticed a feeling of enlarged abdomen and as a result of internal examination at our hospital, he was deemed to have an IgMK-type macroglobulinemia.

In May 1979, he was admitted to our hospital for a further thorough internal examination and was then diagnosed as having primary macroglobulinemia. In August, 1979, multiple ulcers developed on his lower legs. The ulcers continued to appear and disappear repeatedly without any treatment. In October 1979, the ulcers increased and were exacerbated, because of which he was referred to our dermatology clinic on October 11, 1979.

On examination, multiple ulcers the size of a hen's egg to a broad bean were noted on the right lower leg, whereas those on the left lower leg were nearly healed, leaving pigmentation. At the time of this examination, no swelling of the superficial lymph nodes and no mucosal hemorrhage were observed, nor were there any complaints of low back pain or bone ache.

Laboratory values at the time of admission to our hospital in May 1979 indicated an increase in monoclonal serum IgM (Kappa type) up to 5.2 g/dl and 19S component (M protein). Monoclonal IgM-type cryoglobulin was detected in serum and urinary Bence-Jones protein was negative. Bone marrow aspiration showed a proliferation of the plasmoblasts. The T cell percentage was 97.5% (normal, 65–85%) and B cell was 2.0% (normal, 35–15%) in serum. The RBC count was 423×10^4 and rouleaux formation was detectable. The WBC count and sedimentation rate were normal. ESR was 110 mm per hour. The thrombocyte count was 20×10^3 and prothrombin time 12 sec.

Immunoelectrophoresis revealed IgMK-type M protein and K/L=1.41 was noted. The ultracentrifugal pattern showed an increase in the 19S component. A biopsy specimen of the rectum showed normal mucous membrane features and no deposition of the amyloid. An abdominal ultrasound examination only revealed hepatosplenomegaly. Liver and renal function were normal. The chest roentgenogram and ECG were normal. A barium enema examination, upper GI tract series with small bowel follow-through, a liver-pancreas scan, bone scan and a computerized tomographic body scan were all normal. The patient was diagnosed as having primary macroglobulinemia, based chiefly on the findings in the bone marrow.

In November 1979 when he consulted our dermatology clinic with a complaint of multiple ulcers on his legs, laboratory studies indicated severe anemia. The RBC count was 375×10^4 and rouleaux formation was detected. Hemoglobin was 12.3 g/dl, the WBC count was normal

and its sedimentation rate was also normal. ESR was 138 mm per hour. The thrombocyte count was 44 100. Total protein was 8.6 g/dl and γ -globulin was 2.85 g/dl (IgA 97 mg/dl, IgG 1989 mg/dl, IgM 3210 mg/dl). Urinary protein and red cells were positive. Renal and liver function were normal. ^{125}I -Clq binding activity in serum was increased to 39% (normal, 15%).

Histology

A biopsy specimen was taken from a relatively fresh lesion on the flexor part of right lower leg. On the surface, ulceration and granulation with parakeratosis were noted; in the upper dermis down to the subcutaneous tissue, marked dilatation of the capillaries was found, with the vessels filled with homogeneous eosinophilic substances. Cell infiltration consisted mainly of small round circular cells; no tumor cell infiltration was observed.

Immunofluorescence

Direct immunofluorescence revealed deposition of IgM as well as of granular C3 in the vessel walls.

Treatment and clinical course

The patient was orally given an anti-hypertensive agent alone under close observation.

In mid-January 1980, he had dysbasia due to severe edema on his lower legs and was rehospitalized. On examination, the ulcers on the lower legs had almost healed, but an extended petechial hemorrhage was noted. At this time, severe anemia, depressed platelet count, and hemorrhage in his eyes, were observed, but there were no abnormal findings in the bone marrow picture, serum total protein, or increase in IgM.

COMMENT

The ulcers on the lower legs of our patient were considered to have not only cutaneous characteristics of macroglobulinemia, but also cutaneous changes of cryoglobulinemia, based on the findings of positive cryoglobulins. Cryoglobulinemia has recently been regarded as being an immune complex disease (4). The findings in our patient's disease such as the marked increase in the blood immune complex level and deposition of C3 in the vessel walls seemed to be consistent with this.

Skin eruption has seldom been observed in primary macroglobulinemia, especially in its early stage (5). Take et al. (8) reviewed 69 cases of Macroglobulinemia Waldenström reported in Japan up to 1973 to establish which cases had skin eruptions and to indicate the frequency of skin eruptions according to morphology. Their report states that the frequency of skin eruptions was 24.6%. The most frequent type of eruption was spotted hemorrhage (11%); no case of ulceration was found. In our

patient, spotted hemorrhage was noted 3 months after the onset of ulceration. On the other hand, it is not uncommon that the Raynaud's symptom is seen in association with ulceration as a cutaneous manifestation of macroglobulinemia (6).

Moreover, it was reported after a review of the literature that most patients with macroglobulinemia who had Raynaud's symptom also had cryoglobulinemia (7). These findings led us to suggest an significant involvement of cryoglobulins in the ulceration in our case. We considered that serum total protein and the variation in IgM amount might correlate with the appearance or disappearance of the ulcers, as well as with the occurrence of spotted hemorrhage, but the results of our examination so far obtained have indicated that there was no ulceration at the time when the total protein and IgM reached their highest levels, also showing a lack of correlation with either remission or exacerbation and occurrence of spotted hemorrhage. These findings suggest that the development of cutaneous conditions such as ulceration and spotted hemorrhage in macroglobulinemia may depend not merely on the level of serum total protein, but also largely on its properties. Judging by the considerable IgM deposits in the vessels, C3 deposition in the vessel walls, and marked increase in blood Clq-binding immune complexes, we believe that the circulating immune complexes which were deposited in the vessel walls or obstructed the vessels constituted the direct cause of ulceration in our patient.

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Multicentric Reticulohistiocytosis: A Case Report

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Abstract. With the present case report we call attention to the clinical entity of multicentric reticulohistiocytosis (MR). Referring to earlier case reports on this rare condition we present the history, clinical and histopathological findings. We stress the importance of revealing possible underlying internal diseases, including malignancies, and also the importance of histological examination of synovium when synovectomies are carried out in patients with arthritis of unknown cause, as arthritis commonly precedes the mucocutaneous lesions by years.

Key words: Polyarthritis; Papulo-nodular dermatosis; Histiocytic multinucleated giant cells of foreign body type

Multicentric reticulohistiocytosis (MR), first described by Weber and Freudenthal in 1937 (see 5), is a rare, generalized disorder of unknown etiology. It has been associated with tuberculosis and thyroid diseases (9), lipid storage diseases (7), and in 24% with malignancies (5). In 1980 Belaich (2) reviewed 70 cases from the literature. Since then only 7 cases have been reported (3, 4, 8, 10).

The condition is characterized by xanthomatous giant cell granulomata involving the skin, the mucous and synovial membranes, and occasionally other organs (1).

The papulo-nodular lesions of the mucocutaneous membranes are preceded in two-thirds of the cases by arthritis, by months or even years. Pruritus is common. Associated symptoms are weakness, weight loss and febrile periods. Females are afflicted more often than males; the mean age of onset is the fifth decade.

The patient to be described is to the best of our knowledge the first case of MR reported from Scandinavia.

CASE REPORT

The patient is a 58-year-old housewife. Rheumatoid arthritis was present among several family members. At the age of 45 she developed a mutilating arthritis, gradually involving almost all joints, necessitating hospitalization in the Department of Rheumatology six times during the last 3 years.

Clinical examinations have shown symmetrical swelling and deformity of the MCP and PIP joints and signs of arthritis in most other joints. Radiograms showed destructive changes.

Laboratory examinations showed ESR elevation, slight anemia, a positive latex RF test, a negative Waaler-Rose test, and negative ANA. Other examinations monitoring hematologic and serologic parameters were within normal limits.

In addition to conventional physical and systemic anti-rheumatic treatment the patient underwent several synovectomies. Unfortunately the synovium was not examined histologically.

In 1981 the patient developed a pruritic papulo-nodular eruption on the back of her hands and fingers. On admission to the Department of Dermatology a few months later she presented myriads of reddish-brown papules and nodules, 2–20 mm in diameter, on the hands and fingers, on the upper chest, upper arms, face, lips and tongue. She had lost weight and suffered from weakness, and presented a crippling arthritis.

During the following weeks some of the lesions involuted spontaneously. A later exacerbation located to the forearms faded after about 4 weeks.

Clinical and laboratory examination did not disclose internal disease or signs of malignancies.

Histopathological findings

Biopsies were taken from lesions on the skin, lower lip and oral mucosa. They were fixed in 4% buffered formaldehyde and embedded in paraffin wax. The sections were stained with hematoxylin and eosin (HE) and periodic acid-Schiff (PAS).

All specimens showed accumulations of large cells with a faint eosinophilic cytoplasm. Many of the larger cells contained multiple nuclei. Most cells had PAS-positive material. In two of the biopsy specimens the histiocytes were found growing in between the collagen bundles of the reticular dermis. In other specimens nodular accumulations of cells were found in the papillary dermis and also down to the subcutaneous tissue.

Other cell types such as lymphocytes and granulocytes were only sparsely present.

DISCUSSION

Reticulohistiocytoma occurs in two clinical distinctive, but histologically indistinguishable forms: a local variety, reticulohistiocytoma, and MR.