Successful Treatment of Neurological Malignant Atrophic Papulosis in Child by Corticosteroid Combined with Intravenous Immunoglobulin

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Malignant atrophic papulosis (MAP) is a rare thrombo-obliterative vasculopathy of unknown origin [1]. The skin, gastrointestinal tract, and central nervous system (CNS) are most frequently affected [2]. MAP occurs most commonly in young to middle-aged adults [3], while a few of cases with MAP in newborns and children have been described. Treatment of MAP is difficult and no consistently effective therapy has been found. Herein, we describe a child with neurological MAP who responded well to combination therapy with corticosteroid and intravenous immunoglobulin (IVIG) infusion.

A 9-year-old boy was admitted to hospital in November 2010 with a 4-year history of asymptomatic papules and right eyelid ptosis for 1 year. The patient is the first-born male of nonconsanguineous parents. There was no family history of note. In 2006, several erythematous papules appeared on his legs and later scarred spontaneously leaving central white atrophy. Afterward, similar skin rashes presented gradually over the years. Two successive biopsies of lesions on the left leg and trunk showed epidermal atrophy with hyperkeratosis, liquefaction degeneration of the basal cell layer, and zones of mucin deposition in dermis. Thus, the diagnosis of MAP was made. Aspirin and Salvia Miltiorrhiza therapy was initiated from August 2009, but stopped in August 2010 due to stomach upset and thrombocytopenia. In November 2009, the patient developed right eyelid ptosis with mild visual impairment. In September 2010, the patient presented to the

emergency department with a sudden dizziness, several episodes of nausea and vomiting, as well as malaise and difficulty to walk. Magnetic resonance imaging (MRI) of the brain disclosed bilateral subdural fluid collection in the fronto-temporo-parietal regions. Cerebrospinal fluid (CSF) analysis revealed a high protein concentration and white cell count. The symptoms disappeared after emergency treatment with mannitol and antibiotics.

The patient was transferred in November 2010 to our hospital because of progression of skin rash and aggravation of right eyelid ptosis. Dermatologic examination revealed multiple papules ranging from 3 to 6 mm in diameter with an atrophic, porcelain-white central zone and a surrounding erythematous border over the neck, trunk and limbs (Figure 1B). Ophthalmological examination showed right eyelid ptosis and pupil partially obstructed (Figure 1A). A neurological examination revealed no abnormalities. Laboratory investigations including full blood count, coagulation function, biochemistry profile, antinuclear antibody, antineutrophil cytoplasmic antibody, anticardiolipin antibody, serum immunoglobulin, and T lymphocyte subsets were unremarkable. Brain MRI still showed bilateral subdural fluid collection in the fronto-temporo-parietal regions (Figure 2A). Magnetic resonance angiography (MRA) revealed occlusion of the left middle cerebral artery in the medial section with distal collateral circulation formation (Figure 1D). CSF analysis showed significantly elevated protein at 2272 mg/L (normal 150–450), high IgG synthesis rate,

Figure 1 (A) Right eyelid ptosis; (B) Multiple papules with an atrophic, porcelain-white central zone, and surrounding erythematous border on the trunk; (C) Skin biopsy: epidermal atrophy with focal liquefaction degeneration of the basal cell layer, proliferation and endothelial swelling of small vessels in dermis, and perivascular infiltrate of mononuclear inflammatory cell; (D) MRA: occlusion of the left middle cerebral artery in the medial section with distal collateral circulation formation.

and oligoclonal bands. Chest X-ray, electrocardiogram, and ultrasonography of abdomen were otherwise normal. Gastroduodenal endoscopy disclosed a mild chronic and superficial gastritis and duodenitis. Colonoscopy did not reveal mucosal lesions. A third skin biopsy was performed and confirmed the diagnosis of MAP (Figure 1C).

In addition to aspirin 300 mg per 24 h, the patient was treated with oral methylprednisolone on dosage of 32 mg per day (1 mg/Kg). The patient improved gradually over the ensuing 2 months, and CSF analysis revealed protein concentration at 900 mg/L, normal IgG synthesis rate, and no oligoclonal bands. So we started to reduce the dosage of methylprednisolone. However, the protein level in CSF increased again to 1740 mg/L when methylprednisolone was tapered to 26 mg/day. Therefore, IVIG monthly infusions were administered at a dosage of 2 g/Kg (0.4 g/Kg/day for five consecutive days) for 6 months. The patient's condition improved progressively, with neither new skin lesions nor neurological symptoms. Brain MRI was rechecked in April 2012 and revealed a decrease in subdural fluid collection in the

fronto-temporo-parietal regions (Figure 2B). CSF analysis showed protein level at 1120 mg/L. Currently, the patient is undergoing periodic follow-ups, and the dosage of methylprednisolone has been tapered to 12 mg/day.

Malignant atrophic papulosis was first described by Köhlmeier in 1941 and recognized as a distinct clinical entity by Degos in 1942. Currently, fewer than 200 cases have been published in the literature [1]. The etiology of MAP remains unknown, although suggested causes include infection, genetic predisposition, autoimmune, and coagulation disorders [4]. And, the three most accepted theories about the pathogenesis of the disease are vasculitis, coagulopathy, and primary dysfunction of the endothelial cells [1].

In most cases, the diagnosis of MAP is established by the characteristic skin lesions [1]. Usually, skin lesions are asymptomatic and appear in crops, consist of 0.5–1 cm large papules with an atrophic porcelain-white center encircled by an erythematous rim, mostly on the trunk and the upper limbs [1]. Systemic involvement generally follows skin manifestations within weeks to years; in rare

Figure 2 Brain magnetic resonance imaging: (A) bilateral subdural fluid collection in the fronto-temporo-parietal regions; (B) decrease in subdural fluid collection compared with A.

instances, it may precede the skin lesions [2]. The gastrointestinal tract is most frequently involved at a percentage from 50% to 61% in systemic MAP [2]. CNS is affected in about 20% of cases of systemic MAP [5]. Generally, the pathology of CNS involvement in MAP includes disseminated occlusive vasculopathy and the resulting diffuse ischemic changes; clinically, reported neurological features include ischemic and hemorrhagic stroke, disabling polyradiculoneuropathy, neurogenic bladder, ascending thoracic myelopathy, subdural effusion, facial and acral paresthesia, hemiplegia, paraplegia, epilepsy, or nonspecific neurological symptoms [2,6]. Eye involvement including atrophic lesions of eyelids and conjunctiva, telangiectasia of the conjunctival vessels, choroidal infarcts, oculomotor nerve palsy, diplopia, ptosis, papilloedema, optic atrophy, visual field defects, posterior subcapsular cataracts, and optical neuritis is not rare, which can be resulted from both direct ocular involvement and progressive CNS alteration [6]. Other organs that may be involved include heart, pleura, lung, liver, kidney, and oral cavity, but with a lower incidence.

Systemic MAP has a poor prognosis, and the most common causes of death were sepsis from peritonitis (61%), CNS bleeding (18%) and pleural or pericardial involvement (16%) [7]. However, approximately 15% of patients with MAP have a benign course with no systemic involvement and favorable long-term survival. Thus, Heymann suggested reclassification of MAP in 2009 as classical MAP with systemic manifestations and benign cutaneous MAP if lack of systemic manifestations after 3 years [3].

No specific laboratory test can be used to aid in diagnosing MAP [2]. Accordingly, the diagnosis of MAP is mainly based on the clinical and histological findings. The characteristic histological features of both the skin and systemic lesions are endothelial proliferation with thrombosis and occlusion of small and medium blood vessels resulting in tissue infarction [3].

Despite pilot studies, there is no standard effective treatment for MAP [1]. Anticoagulants and antiplatelet agents, which might prevent platelet aggregation before thrombus formation and inhibit disease progression [4], can be used as a first therapeutic approach on a newly diagnosed patient with MAP [1]. Other dif-

ferent therapies, including systemic corticosteroids [4,8], cyclophosphamide [4] IVIG [9] and so on, have been tested without consistent results.

The diagnosis of MAP was easily made as our patient showed typical skin lesions and histopathological changes. Further deterioration of the disease (CNS manifestations) occurred during the treatment with anticoagulant and antiplatelet. We decided to treat the patient with systemic corticosteroid after careful consideration that MAP is pathologically a noninfectious and inflammatory vasculitis. Both the symptom and the protein content in CSF were improved within the following 2 months. However, an elevated protein concentration of CSF reappeared in tapering schedule of corticosteroid. At this time, we induced IVIG therapy which is used off-label for a large number of chronic inflammatory diseases including some autoimmune diseases [10], and the result is positive.

Malignant atrophic papulosis is a rare and potentially life-threatening disease. Systemic corticosteroids combined with

IVIG infusion could be adopted, considering the possible autoimmune pathogenesis of MAP and the lack of efficacy with conventional therapy such as anticoagulants and antiplatelet agents.

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Conflict of Interest

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no competing interests exist. The patient had signed the informed consent for this study and publication.

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