

CASE DISCUSSION-JUVENILE DERMATOMYOSITIS

CASE HISTORY

A 6 year old female child is brought to your clinic with a 3 month history of a red rash on her knuckles. It had been seen 2 months before by a family doctor who diagnosed a contact allergy and prescribed a corticosteroid cream. The rash has persisted and recently worsened. She has stopped riding her bike and now is having trouble climbing the stairs at home. Her father has had to help her walk in the afternoon due to leg pains and has even carried her in his arms. Her parents have noted a fever of 38.5-39 degrees Centigrade on three occasions in the past month. She has developed a rash on her cheeks. She has choked on a piece of hamburger recently.

Initial physical examination reveals a child with a red macular rash on her cheeks and eyelids. She has red papules on all of her MCP's and PIP's and abnormal nailfold capillaroscopy. Her right knee is swollen. She cannot do a situp or hold her head up against gravity. She has a nasal speech pattern and a positive Gower's sign.

She is admitted immediately to your hospital. She is noted to have trouble with her secretions and has a decreased tidal volume.

Issues:

- 1) What workup would you perform?
- 2) What treatment would you initiate?
- 3) What prognosis would you discuss with the parents?
- 4) What tests and/or outcome parameters would you follow to measure disease activity?
- 5) What would be your 2 year plan of treatment?

DISCUSSANT #1

On admission, we would like to get an insight in the severity of the dermatomyositis of this six-year-old. Clinically, the skin manifestations are present, with the typical facial rash and the Gottron's papules, together with other signs of cutaneous vasculopathy. Muscle involvement is also prominent with progressive proximal and distal muscle weakness, difficulties swallowing and an altered speech. In our department, the degree of muscle involvement is assessed by isometric handheld dynamometry (HHD), the Childhood Myositis Assessment Scale (CMAS) and endurance, which is tested by a maximal exercise test using a motor-driven treadmill.

Disease activity is assessed biochemically by a full blood count, erythrocyte sedimentation rate and especially by the elevation of muscle enzymes as CK, LDH, AST and APT. An immunological workup includes determination of ANA, extractable nuclear antigens and myositis-specific autoantibodies. There is an ongoing discussion about the need for a muscle biopsy, performed under general anesthesia, to confirm the diagnosis, especially in patients with an impaired lung function. A STIR MRI with fat suppression can be scheduled in order to determine the degree of muscle involvement. To assess the involvement of other organ systems, a cardiac ultrasound is planned, together with an esophageal manometry, especially in the case of difficulties swallowing. Examination of stool, to detect occult bleeding, and a urine sedimentation has to be done. An abdominal ultrasound is performed to determine the size of the liver and spleen and the state of the abdominal vessels. To exclude retinal vasculitis, a fundoscopy is scheduled.

As soon as possible, treatment should be initiated. The symptoms of this girl are indicative for a more severe disease, with evidence of vasculopathy and decreased muscle strength. At present, the initial therapy is prednisone 2 mg/kg/day orally in combination with calcium and vitamin D supplementation. For more severe disease, as in this patient, we should advise to give steroids intravenously in multiple daily doses, because of the possibility of impaired abdominal absorption due to vasculitis. In severe, life-threatening disease, intravenous methylprednisolone pulse therapy (15-30 mg/kg/dose for 3 days) is thought to induce a rapid improvement of severe dysphagia, myocarditis and in individuals who have rapidly worsening muscle weakness. As a cut-off value, we consider a CMAS score below 24, being 45% of optimal performance, as a risk for trauma such as tripping over, falling without protection of arms, aspiration, etc. When the initial treatment with steroids appears to be ineffective after 4 weeks or if we are not able to taper off the prednisone, a second line immunosuppressive agent should be added. Use of methotrexate (MTX) early in the disease is currently first choice, with a dosage of 1mg/kg intravenously, once weekly. We avoid subcutaneous or intramuscular administration because we consider this administration a risk for inducing ulceration or calcifications. When using MTX, potential adverse effects such as photosensitization, oral ulcers or opportunistic infections should be monitored. The initial response usually occurs between 4 to 8 weeks after starting this therapy. Intravenous immunoglobulin has been reported to have benefit in combination with the ongoing treatment in resistant disease, however iv immunoglobulin therapy is very expensive and not evidence based.

As important as the pharmacological therapy, is the physical therapy program to preserve, and if possible, improve existing muscle function, to prevent disuse atrophy, to avoid joint contractures and to restore the aerobic capacity of the chronically ill child. In the early phase of the disease, it is sufficient to encourage children and parents to maintain ADL, because of serious risk of inflicting trauma to an inflamed muscle when stretching in an active phase. In our Physical Therapy Department, special programs, including aquatic training, are

implemented after the initial phase of muscle edema and general malaise with emphasis on muscle flexibility.

In the discussion with the parents, the severity of the disease has to be stressed. We would explain that JDM is a rare, mostly chronic disease, with an unknown etiology. The prognosis has improved since the start of corticosteroids and other immunosuppressive agents. The course of the disease is difficult to predict, but is known to have a long course with remissions and exacerbations or, in some cases, a chronic course with a severe debilitating morbidity. The presence of dysphagia, dysphonia, cutaneous vasculitis and severe decreased muscle strength are indicators of serious disease. We would discuss that the use of immunosuppressive therapy is warranted and that this can have concomitant side-effects, which would be followed-up and treated if necessary. Finally, the possibility of calcifications should be discussed, with a decreased frequency due to early aggressive treatment.

In the beginning of the treatment, the girl will be admitted in order to assess the response to the treatment and to start physical therapy. The global assessments of the patient and physician, which each integrate a number of facets of disease activity from different perspectives play a major role in assessing the therapeutic response in combination with the more objective parameters as discussed before. In case of unsatisfactory response to the steroids, second line agents will be added to the therapy.

Prednisone dosage is tapered after 4 to 6 weeks, to avoid steroid myopathy. In the course of the disease, disease activity will be followed clinically on regular outpatient clinic visits, as well as by laboratory measures and assessment of the muscle parameters. It is well known that muscle enzymes and BSE can be normal even in active disease, so these are no perfect parameters during follow-up. It has been suggested earlier to measure von Willebrand factor antigen to assess the degree of endothelial inflammation, but we think it is not helpful in evaluating the disease activity in an individual patient. Muscle strength, muscle function and endurance can be assessed in time in a quantitative manner. When indicated, the tests to exclude other organ involvement, discussed earlier, are repeated.

The aim is to taper the steroids further, to a minimal dose. Then, in the case of stable disease, the MTX treatment can also be diminished.

Part 2

Two years later the rash is still active but the muscle strength and muscle enzymes are normal. The child has developed sheets of calcium deposits in her forearms and arms.

Issues:

- 1) In general, would you treat aggressively with immunosuppressives if the rash is active but the muscle strength is normal?
- 2) How would you address the calcification problem?

Answer:

First it is important that all the muscle modalities [muscle strength as well as (an-) aerobic performance] and muscle enzymes are normal. Then, we would not treat the skin manifestations aggressively if there is no indication of severe cutaneous vasculitis. Usually, we start with hydroxychloroquine at an oral dose of 5 mg/kg/day. Monitoring is needed for potential retinal toxicity.

Regularly we treat the skin locally with a cream based on corticosteroids but there are new interesting developments for local treatment like a cream based on FK-506 (tacrolimus). Until now, there is not enough evidence for this local treatment. For the treatment of calcifications there are no controlled therapeutic trials, and there can even be a spontaneous, unpredictable regression. We suggest to start treatment with the oral calcium antagonist Diltiazem, at a dose of 2 mg/kg/day, increased to 5 mg/kg/day after 3 to 4 weeks. The therapeutic effect is expected after several months. In case of severe calcinosis, a combination treatment with bisphosphonates is started. Oral alendronate (< 1 m² BSA: 10 mg/day; > 1 m² BSA: 20 mg/day) can be added to the therapy with control of serum levels of calcium, phosphorus, alkaline phosphatase and the urinary calcium/creatinine ratio.

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References

- 1.Pachman LM. Juvenile dermatomyositis. Pathophysiology and disease expression. *Pediatr Clin North Am* 1995;42:1071-98.
- 2.Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. *Rheum Dis Clin North Am* 2002;28(4):833-57.
- 3.Takken T, et al. The physiological and physical determinants of functional ability measures in children with juvenile dermatomyositis. *Rheumatology* 2003;42:158-62.
- 4.Reed AM, Lopez M. Juvenile dermatomyositis. Recognition and treatment. *Pediatr Drugs* 2002;4(5):315-21.
- 5.Oliveri MB et al. Case Report : Regression of calcinosis during diltiazem treatment in juvenile dermatomyositis. *J Rheumatol* 1996;23:2152-55.

DISCUSSANT #2

INITIAL INVESTIGATIONS:

To assess the degree of muscle involvement, a formal muscle assessment is important. This centre uses the childhood myositis assessment scale (CMAS), as well as the MMT8 (eight muscle manual testing) pending validation of these scores. An MRI of thigh muscles will provide evidence of inflammatory changes in the fat, fascia and muscles. An open biopsy is performed in this hospital, though it may not be necessary for diagnostic purposes if the MRI is abnormal. A needle biopsy is not advisable because of the small sample and, as the disease is often patchy, it may be normal. Muscle biopsies stained by conventional histopathology techniques may be normal in early disease with very few/no inflammatory cellular infiltrates present. She should also have a Child Health Assessment Questionnaire (CHAQ) to assess her function and quality of life (to be filled in by her parents). The blood work up should include full blood count, ESR, CRP, muscle enzyme such as creatinine kinase and LDH, U&E's, LFT's, ANA, ENA, and if possible specific auto antibodies (such as Jo 1 and RMP), to exclude overlaps and other rare muscle diseases. Her nasal speech may be associated with swallowing difficulties and a video fluoroscopy is advisable. Assessment of other organ involvement includes pulmonary function and chest radiograph. If abnormal, a high resolution fine-cut CT scan is needed to delineate any inflammatory lung disease (ILD).

TREATMENT:

IV Methylprednisolone, at 30mg per kilo per dose on day one, two and three is our current practice to achieve an immediate and sizable anti-inflammatory response. This may be repeated the following week. In between the IV Methylprednisolone, she should have 0.5-1mg per kilo orally of Prednisolone. If the child did not respond dramatically to the IV MP, or there is evidence of malabsorption or GI vasculitis (symptoms such as abdominal pain), the equivalent dosage of prednisolone should be given as MPIV. A switch to oral administration will be later, once the symptoms improve (usually after 1-2 weeks). For medium to long-term control of disease activity, methotrexate is given sc after discussion with the parents, the child, and the primary care physicians. The starting dose given here is 15mg per m². If the CT scan showed any signs of lung abnormalities (alveolitis or fibrosis), IV Cyclophosphamide at 500-750/m² and at monthly intervals for the first six months is advisable as well as methotrexate.

PROGNOSIS:

With this child one should discuss the spectrum and the disease course for dermatomyositis (unicyclic, polycyclic or continuous). In this case, the possible ILD suggests a poorer prognosis, and she is likely to be in the continuous or polycyclic group. The types of therapy will be discussed and in view of her poorer prognosis, the emphasis will be biased towards more aggressive treatment. Controlling the disease is of paramount importance, in order for the child to have no long-term sequelae once the disease has gone into remission.

MEASURES OF DISEASE ACTIVITY AND OUTCOME:

To assess muscle disease activity, the CMAS and MMT8, and CHAQ are used in this unit, MRI scans are done at 6 monthly intervals or with a disease flare. Clinical observation of the presence of arthritis, rash, or oedema is an indicator of disease activity. Calcinosis is an indicator of severe disease activity. CK and LDH are useful indicators of initial response to therapy, and of flares of disease. However CK may not be as good a marker of muscle inflammation as LDH, especially later on in the disease with significant loss of muscle bulk. MRI is often useful in these cases. Video fluoroscopy and lung function test should be also used to monitor progress of the lung disease, with a CT scan at appropriate intervals.

PLAN OF TREATMENT at 2 years:

The critical issue is whether there is subacute inflammation that has contributed to the sheets of calcinosis, despite the normal CK. Disease activity is also suggested by the prominent rash. An MRI of the proximal muscle groups would be essential. If there is active muscle inflammation, as well as lung involvement, cyclophosphamide should be started. In this unit, IV is preferred as there are no concerns with compliance, absorption, or hydration, and there appear to be fewer long-term side-effects. A change to cyclosporin A orally is unlikely to be effective at this stage, but combination therapy may be worth a try for a limited period. If the child's disease has progressed despite 6 months' of cyclophosphamide, then more experimental treatments such as anti-TNF should be considered. Pamidronate for the calcinosis is worth considering, and our unit has had 3 patients who have responded well to this combination between 6 months and 1 year.

ACTIVE RASH WITH NORMAL STRENGTH AND NO EVIDENCE OF MUSCLE

INFLAMMATION:

These children can pose a difficult problem. The rash is indicative of active disease but does not always respond as well to the same medication as the muscle inflammation. Ongoing disease is often seen in these children as they are also often underweight and growth retarded. Different medications such as pulses of IVIG, Hydroxychloroquine/mepacrine or Tacrolimus may be helpful.

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