Case report

Juvenile dermatomyositis forty years on: Case report

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Abstract

We present a case report of a 42 year old female, diagnosed at the age of 3 with Juvenile Dermatomyositis. The clinical course was severe and refractory to immunosuppressive therapy. Currently, she is mostly affected by severe muscle atrophy, large joint contractures, calcinosis, and a lipodystrophy associated metabolic syndrome with hypertriglyceridemia, insulin resistance, high total testosterone and hepatic steatosis. She developed Hodgkinś lymphoma in the course of her disease. Personalized therapeutic choices are discussed as regards juvenile dermatomyositis complications.
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1. Introduction

Juvenile dermatomyositis (JDM) is an autoimmune disease resulting in perivascular inflammation, perifascicular atrophy and muscle degeneration [1,2] and represents 85% of the idiopathic inflammatory myopathies in childhood [3]. Novel autoantibodies associated to specific clinical phenotypes have been described in the past decade. Amongst these, anti-p155/140 – targeted to transcriptional intermediary factor 1 gamma (TIF1-γ) and anti-p140 – targeted to nuclear matrix protein 2 (NXP2), are more likely to occur in children with calcinosis and cutaneous ulceration [4–6].

Fifty years ago, active treatment of childhood onset JDM resulted in much improved prognosis [7]. Despite progress, standard of care still remains confined to untargeted immunosuppressive therapy with steroids [8]. As recently reviewed [9], the use of steroid sparing agents is recommended, usually with methotrexate, but also azathioprine and cyclosporine,

intravenous immune globulin, tacrolimus, rituximab and cyclophosphamide in refractory cases. Cardiac or respiratory involvement lower 10–year survival rates, otherwise reported to be over 90% [10,11]. Many children therefore survive to adulthood, but there are scarce descriptions of disease activity, co-morbidities and functional status after prolonged disease. Aiming to contribute to disease knowledge we report an adult patient with JDM exhibiting lipodystrophy, ongoing calcinosis, and irreversible joint contractures, in whom a prior diagnosis of malignancy restricts therapeutic choices and whose management remains an ongoing challenge.

2. Case report

The female patient, currently 42 years-old, was admitted to the Hammersmith Hospital in London, at the age of 3. At that time, major complaints were proximal muscle weakness with Gowers sign, unilateral facial nerve palsy and ulcerating skin lesions (Fig. 1a–d). The electromyography of right deltoid, triceps and tibialis anterior muscles revealed short, small amplitude polyphasic potentials, with no spontaneous activity at rest. The diagnosis of JDM was made on the basis of needle biopsy of left quadriceps displaying vacuolar

Fig. 1. Dermatomyositis; vasculitic ulcers; recurrent contractures. This girl was first seen at 3 years of age with an 8-month history of weakness, skin rash and misery, with progressive flexion contractures of the hips (a) and knees (b). She responded well to steroids and was rehabilitated with active physiotherapy. She was readmitted from abroad 8 months later with marked vasculitic ulcers in the axillae, which gradually resolved (c) and (d). She later had recurrent relapses and remissions with adjustment of therapy. At 7 years of age she stopped walking after formation of a large haematoma in the right thigh. She was again rehabilitated with active physiotherapy (e). There was still active skin rash and some facial weakness with limited eye closure (f). She was still ambulant 15 months later but had considerable weakness and fixed equinus (g). She had lost weight and had very little muscle bulk. Text and Images reproduced with permission from Muscle Disorders in Childhood, 2nd Ed. By V. Dubowitz. 549 pp., illustrated. Philadelphia: W.B. Saunders, 1995.

appearance of several muscle fibers and perifascicular atrophy (Supplementary Fig. 1).

From the time of diagnosis, treatment consisted of a steroid regimen, initially given alone and subsequently combined with azathioprine, followed by cyclosporine. From the onset of the illness, periods of immobility were followed by major joint contractures and over the next few years she was regularly admitted to hospital for periods of intensive physiotherapy which were extremely successful (Fig. 1e–g). Of note, there was no history of consanguinity, episodic fevers, seizures, anemia, respiratory difficulties or learning disabilities and she successfully completed a university degree.

Overall, response to treatment was poor and by the age of 21 she was wheelchair bound and immunosuppressive therapy was stopped. Even though the episodes of cutaneous ulceration no longer occurred, several other features developed over the next years namely an erythematous pruritic and progressively more indurated facial skin, generalized calcinosis and intermittent diarrhea, the latter attributed to intestinal bacterial overgrowth syndrome. Nodular-Sclerosis Classical Hodgkin Lymphoma (stage II, supra-diaphragmatic, category B) was diagnosed at age 31, with full remission after six cycles of chemotherapy consisting of doxorubicin, bleomycin, vinblastin and dacarbazine. There was no serological evidence of acute Epstein-Barr virus infection (virological status in lymphoma cells was not evaluated). She did not tolerate a cyproterone/ethinylestradiol combination pill due to dysmenorrhoea.

At the age of 38 she was re-evaluated in our Autoimmune Diseases Unit. She complained of menstrual irregularities, hirsutism and relentless calcinosis. She exhibited low stature, diffuse alopecia, poikiloderma in a photosensitive distribution, symmetric parotid hypertrophy, periungueal telangiectasia, livedo reticularis (over the trunk and anterior thighs) and multiple atrophic scars corresponding to areas of previous ulceration. There were fixed contractures of the major joints (shoulders, elbows and knees), lumbar scoliosis, generalized muscle atrophy and multiple foci of calcinosis along the muscle fascia of limbs and trunk. The abdomen was disproportionately large and corresponded to a most striking lipodystrophy with absence of fat in the face and limbs (Fig. 2). There was no cervical weakness, no difficulty in speaking or in swallowing. She was able to move her upper limbs, pick up small objects and feed herself.

Laboratory evaluation revealed normal creatine kinase and aldolase, increased total serum testosterone of 71 ng/dL, (normal values 10,8–56,9 ng/dL), but normal levels of serum thyroid stimulating hormone, prolactin, androstenedione, basal 17-hydroxy progesterone, estradiol, FSH, LH, ACTH and serum cortisol levels. Her fasting plasma glucose (69 mg/dL) and Peptide C (6,5 ng/mL, normal range 0,9–7.1 ng/mL) were normal but insulin was increased to 65,5 uUI/mL (normal range 1,9–23 uUI/mL). She also had hypertriglyceridemia (1860 mg/dL, normal range < 150 mg/dL) and low levels of high density lipoprotein cholesterol (28 mg/dL, normal range < 130 mg/dL). Liver transaminases were normal but the gamma-glutamyl transferase was 3 fold elevated; ANA testing was intermittently positive, with a low title (1/160) but no specific positivity was found; there was no lung parenchymal change in the chest radiograph which displayed multiple calcifications in the subcutaneous tissues; the echocardiogram was normal; no structural abnormality or pressure changes were detected by Doppler echocardiography and nailfold video-capilaroscopy revealed a late-scleroderma pattern (Supplementary Fig. 2). Magnetic resonance imaging (MRI) showed diffuse muscle fatty atrophy (Grade III–IV) of masseters, shoulder girdle, deltoids, paravertebral thoracic, gluteal and thigh groups. The only relatively preserved muscles localized to the neck, thighs (adductor magnus and vastus intermedius) and legs (tibialis anterior and posterior and toe extensors). There was no sign of muscle inflammation on fluid sensitive sequences (STIR and T2-weighted images). Parotid glands were heterogeneous with fatty infiltrates and diffuse calcifications. There was a marked increase in posterior cervical, axillary, mediastinal and intra-peritoneal fat deposition, also asymmetrically localized to the anterior and lateral portion of both thighs (Fig. 3). Small areas of subcutaneous oedema were suggestive of panniculitis in thighs and legs. Hepatomegaly was noted with splenomegaly, normal kidneys, uterus and ovaries. There was no lymphadenopathy. No mutations were found in the genes *LMNA, ZMPSTE24, PTRF, CAV-1, AGPAT2, BSCL2, PPARG, INSR, PLIN1, CIDEC, PIK3R1, NSMCE2, POC1A, PCYT1A, POLD1* or *PSMB8*. Soon after the genetic tests were performed, the patient's serum tested positive for anti-transcriptional intermediary factor gamma protein antibody (TIF1-gamma) (Euroimmun®-Lübeck, Euroline scan software, patient intensity 15, control 99), supporting the original diagnosis. There was no reactivity against the following antigens: Mi-2 (nucleosome remodeling deacetyalse complex), MDA (melanoma-differentiation associated gene 5), SRP (54 kDa, signal recognition particle), NXP-2, SAE (small-ubiquitin-like modifier activating enzyme), Ku, PM-Scl (75 and 100 kDa), Jo-1 (histidyl-tRNA synthetase), PL-7 (threonyl-tRNA synthetase), PL-12 (alanyl-tRNA synthetase), EJ protein (glycyl-tRNA synthetase), OJ (isoleucyl-tRNA synthetase) and Ro-52KD.

Following re-assessment, weekly s.c. methotrexate (up to 20 mg/week) and quarterly i.v. Pamidronate failed to have a positive impact on the rate of calcinosis deposits and range of metabolic abnormalities. The latter was associated with an episode of renal colic and both were discontinued after two years. Since then, painful calcium deposits have been removed surgically on three occasions. She has not tolerated metformin due to side-effects and is poorly compliant with fenofibrate. Decreased gastrointestinal absorption may also contribute to a poor response to therapy and serum triglyceride concentrations are usually 5–6 fold elevated. She reports beneficial anti-diarrheal effects with VSL#3®, a commercially available probiotic, taken as required. Apart from feeling that the skin around her face is tighter there has been no change in her clinical features over the past four years. She is partially dependent for her hygiene needs which restrict her social life but is otherwise independent in her daily activities with an electric wheelchair and adapted motorized vehicle. She undertakes physiotherapy sessions consisting of passive limb mobilization three times per week.

3. Discussion

JDM is a very rare condition with an incidence of 2–4 cases per million per year, mostly affecting females. In so much as the peak incidence occurs between the ages of 5–10, up to 25% of patients experience disease onset before the age of 4 [12], similarly to our patient. The disease may remit, relapse or follow a chronic continuous form [13]. When
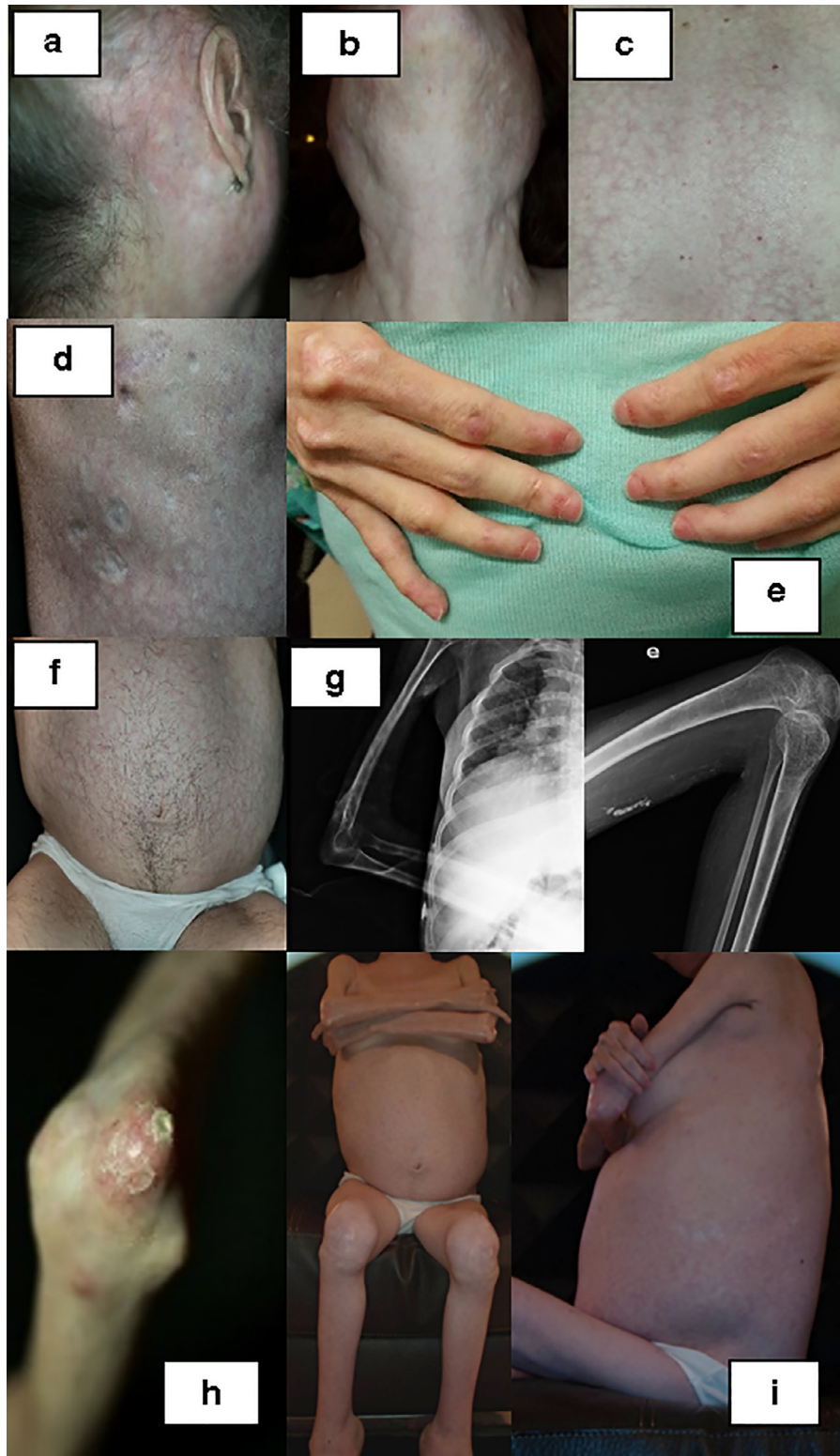
Fig. 2. Clinical features of the patient as an adult: poikiloderma and skin tightness (a); parotid hypertrophy (b); livedo reticularis over dorsum (c); atrophic scars (d); periungueal telangiectasia (e); hirsutism (f); calcinosis in fascial planes and joint contractures (g); cutaneous calcinosis (h); lipodystrophy with abdominal redistribution of fat and muscle atrophy (i).
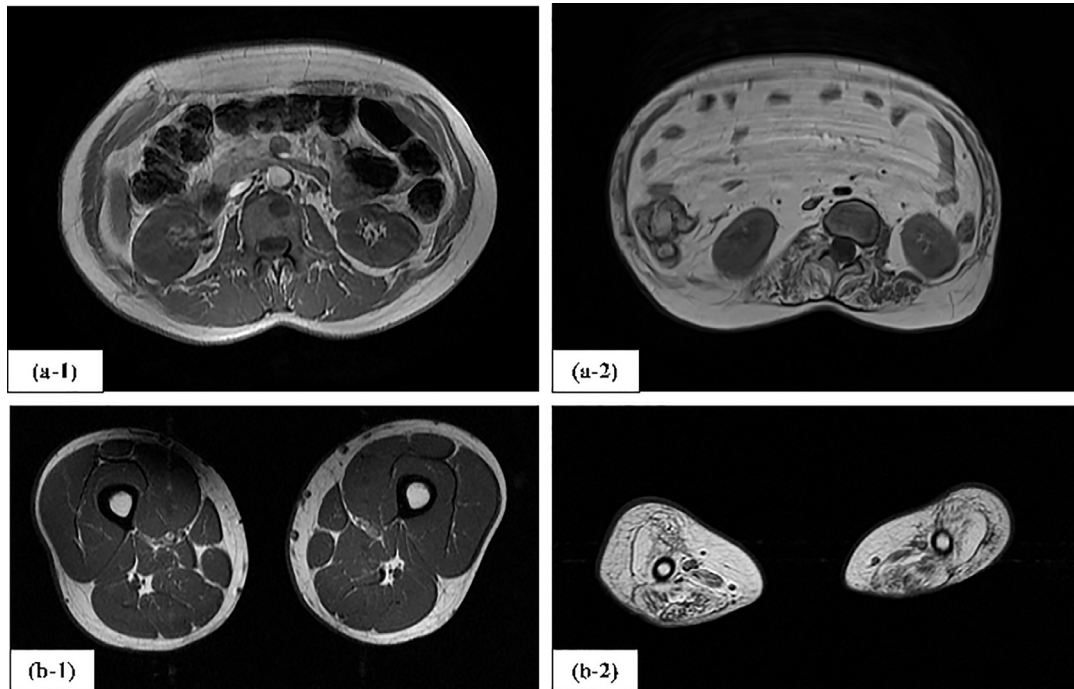
Fig. 3. MRI T1-weighted axial images from the abdomen (a) and thigh (b), from a healthy subject (1) and from the patient (2) where the massive increase in fat is mainly intraperitoneal but also assymmetrically distributed throughout the thigh circunference. There is marked (Grade III–IV) diffuse thigh muscle atrophy.

compared with adult auto-antibody reactivities, anti-TIF1-γ positive children are more frequently affected by muscle atrophy, contractures, calcinosis and cutaneous vasculitis [14]. Of note, our patient received appropriate therapy, namely steroids and cyclosporine from disease onset. Physiotherapy treatments were intense but intermittent, with prolonged periods of immobility. Recurrent contractures developed from early on in the course of disease.

Several complex complications developed as disease progressed. Lymphoma developed in adulthood, many years after disease onset. In a recent literature review lymphoma was very rarely diagnosed in juvenile dermato/polymyositis, occurred only after the disease was well established and all the patients suffered from the non-Hodgkinś lymphoma type [15]. Hodgkin lymphoma (HL) has been described in non-immunosuppressed individuals but HL-like conditions have also been described in the spectrum of post-transplant lymphoproliferative disorders [16]. After a ten year-lapse, a relationship to prior immunosuppressive therapy remains an elusive possibility in our patient.

Albeit not confirmed, the initial lack of an auto-antibody marker, the presence of marked lipodystrophy, possible panniculitis and lack of muscle inflammation in the biopsy specimen reviewed raised the suspicion of an alternative diagnosis but no evidence of an auto-inflammatory disorder or a muscle dystrophy was found. While the lipodystrophy was suggestive of Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperatures (CANDLE) [17,18], lack of periodic fevers and systemic inflammation made this less likely, whereas the presence of anti-TIF1-γ, muscle atrophy, joint contractures, calcinosis and nailfold changes clinched the diagnosis of JDM.

JDM occurs in genetically susceptible patients [19–22]. Its association with lipodystrophy (deposition of fat in ectopic locations such as in salivary glands, the peritoneal cavity, liver and muscle and absence of fat deposits in other sites) [23,24] and lipodystrophy-associated metabolic abnormalities (hypertriglyceridemia, insulin resistance, high testosterone, hypertrichosis and probable fatty liver disease) has been described with severe calcinosis, joint contractures, muscle atrophy, chronic continuous illness course, facial erythema and anti-TIF1-γ positivity [25,26], all of which were present in our patient.

Follow up of JDM patients into adulthood has demonstrated the overall systemic nature of the disease and its impact on several organs on the long term. Even though studies on a Norway cohort followed over 16,8 years (2–38,1 years) has showed JDM patients often maintain active disease in the long term, our patient mostly suffers from cumulative organ damage, whose main predictor is disease activity at onset [27].

Because of the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin may be low and leptin replacement could be a therapeutic option in our patient, in an attempt to overcome morphological and metabolic abnormalities. However lymphoma after leptin therapy for patients with acquired lipodystrophy has been described [28]. In addition, no single drug or associations of drugs has been effective in

the treatment of calcinosis in JDM [29]. Upregulation of type I interferon pathway, described as a biomarker of JDM disease activity [30] as well as an effector molecule in CANDLE [31], may be a driver of disease pathogenesis. It is tempting to speculate that antagonizing type I interferon could have a favorable therapeutic impact in our patient. Overall, a history of lymphoma, longstanding immune-mediated disease, a potentially vulnerable immune system and the degree of irreversible organ damage lead us to take a conservative "do no harm" approach.

In conclusion we present a patient with a diagnosis of JDM at the age of 3 years, with a partial response to therapy and several co-morbidities. Marked lipodystrophy and little inflammation in the original muscle biopsy specimen raised suspicion of an overlap with muscle dystrophy which was not confirmed. Our key message highlights the extraordinary advances introduced in the 1980ś, reducing patient mortality and side-effects of extremely high dosages of steroids. Despite the presence of disability our patient survived a severe childhood disease and leads a meaningful life.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.06.011.

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