A novel case of TIF1γ autoantibody positive dermatomyositis associated with a non-functional pancreatic neuroendocrine tumor

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Abstract

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal muscle weakness associated with a distinct cutaneous eruption. The association of DM with malignancy has been extensively described in the literature. Patients with DM that also have transcriptional intermediary factor 1γ (TIF1γ) autoantibodies (anti-p155, anti-p155/140) have higher rates of malignancy when compared to those without the autoantibody. We report the case of a 65-year-old woman with TIF1γ autoantibody positive dermatomyositis associated with a non-functional pancreatic neuroendocrine tumor (PNET). Surgical resection of the PNET resulted in significant clinical improvement and a reduction of TIF1γ autoantibody levels in our patient.

Keywords: dermatomyositis, neuroendocrine, pancreatic tumor, TIF1γ, autoantibody, paraneoplastic, transcriptional intermediary factor-1γ

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy that presents with proximal muscle weakness accompanied by a characteristic rash. The relationship between DM and malignancy is well established in the literature, with malignancy identified in approximately 25% of cases of DM [1,2]. The most commonly associated malignancies are ovarian, lung, gastric, pancreatic, and bladder adenocarcinomas [3]. The presence of transcriptional intermediary factor 1γ (TIF1γ) autoantibodies in patients with DM is associated with higher rates of malignancy than those without the autoantibody [4,5]. We report the case of a 65-year-old woman with TIF1γ autoantibody positive dermatomyositis associated with a non-functional pancreatic neuroendocrine tumor (PNET). Surgical resection of the PNET in our patient resulted in significant clinical improvement and a decrease in TIF1γ autoantibody levels. To our knowledge, this is the second reported case of dermatomyositis associated with a pancreatic neuroendocrine tumor and likely the only reported case of TIF1γ autoantibody positive DM associated with a PNET [6].

Case Synopsis

A 65-year-old woman was referred to our tertiary medical center following a diagnosis of dermatomyositis. She reported a four-month history of mylagias, dysphagia, and a pruritic, tender skin

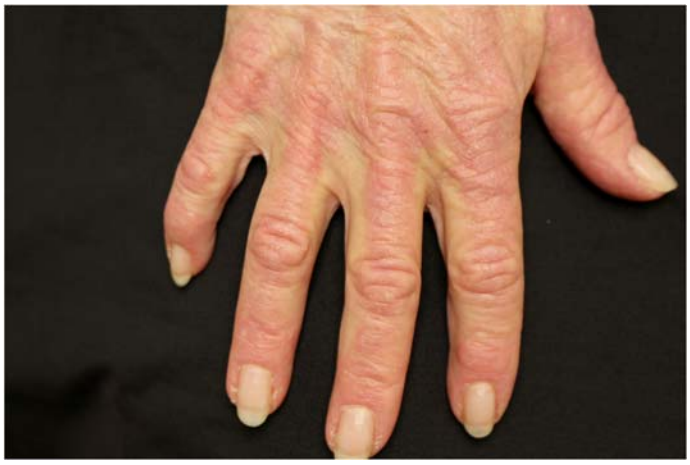

Figure 1. *Violaceous coalescing papules located on the right dorsal hand and fingers.*

eruption. Her medical history was significant for previous diagnosis of systemic lupus erythematosus with ANA positivity 27 years prior to her visit. Her symptoms at the time included malar rash, fever, malaise, oral ulcers, arthralgias, and Raynaud phenomenon. This episode resolved without treatment. Physical examination revealed violaceous coalescing papules located on the ventral and dorsal forearms, hands (**Figure 1**), fingers, right frontal scalp, and upper eyelids. She had red on white poikiloderma on the posterior neck and shoulders but no palatal erythema. A punch biopsy of her left dorsal hand taken by the referring physician revealed an active interface process with thickening of the basement membrane.

Creatine kinase, aldolase, ALT, AST, CRP, ESR, ANA, albumin, and other routine laboratory values were within normal limits. Myositis-associated autoantibody panel (ARUP Laboratories, Salt Lake City UT) revealed positivity for antibodies against TIF1γ. Antibodies against the tRNA synthetases (Jo-1, OJ, EJ, PL-7, and PL-12), NXP-2 (nuclear matrix protein-2), Mi-2 (nuclear helicase protein), and SRP (signal recognition particle) were not detected. A malignancy workup was initiated which included colonoscopy, Pap smear, mammography, transvaginal ultrasound, and chest/abdomen/pelvis CT. The CT revealed a 6×9.5mm pancreatic mass. Further endoscopic ultrasonography and fine needle biopsy of the mass showed morphologic features characteristic of a neuroendocrine tumor. No evidence of metastatic disease was seen on PET scan. The mass was further characterized as a non-functional pancreatic neuroendocrine tumor owing to the absence of clinical findings consistent with a hormonal syndrome (e.g. insulinoma, gastrinoma, or glucagonoma).

She received several months of pharmacologic management of her DM, but this yielded only partial resolution of her symptoms. Treatments included mycophenolate mofetil, hydroxychloroquine, prednisone, methotrexate, hydroxyzine, tacrolimus ointment, and betamethasone ointment. The patient and care team decided to proceed with surgical excision of the mass in light of the sub-optimal response to pharmacologic therapy. Histological evaluation of the excised mass demonstrated a mitotic rate of 1.2/10 high power fields and a Ki-67 proliferation index of 2.2%. Immunohistochemical staining showed positivity for synaptophysin and chromogranin. These microscopic findings along with the previous biopsy were most consistent with a grade 1 pancreatic neuroendocrine tumor (**Figure 2**).

Following the surgery, the patient continued a regimen of mycophenolate mofetil 500mg, hydroxychloroquine 200mg, and tacrolimus 0.1% ointment twice daily. Two days after surgery the patient began to notice improvement in her rash. Two months after removal of the PNET, her myalgias and dysphagia had resolved and her cutaneous manifestations had nearly completely resolved (**Figure 3**). A repeat myositis associated antibody panel showed weak positivity for the TIF1γ antibody.

Case Discussion

Dermatomyositis is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and a distinct cutaneous eruption, classically affecting the hands and face. The diagnosis is often made clinically based on the presence of the specific manifestations of the DM, including a helitrope rash and Gottron papules, in conjunction with the muscle weakness. A muscle biopsy can also be useful in confirming the diagnosis. Malignancy has been identified in approximately 25% of cases of DM [1-3]. DM has been associated

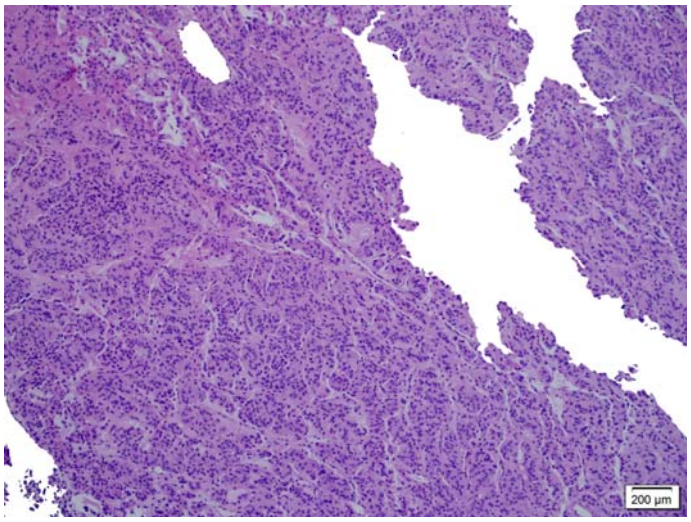

Figure 2. *Section of pancreatic nodule. H&E, 10×.*

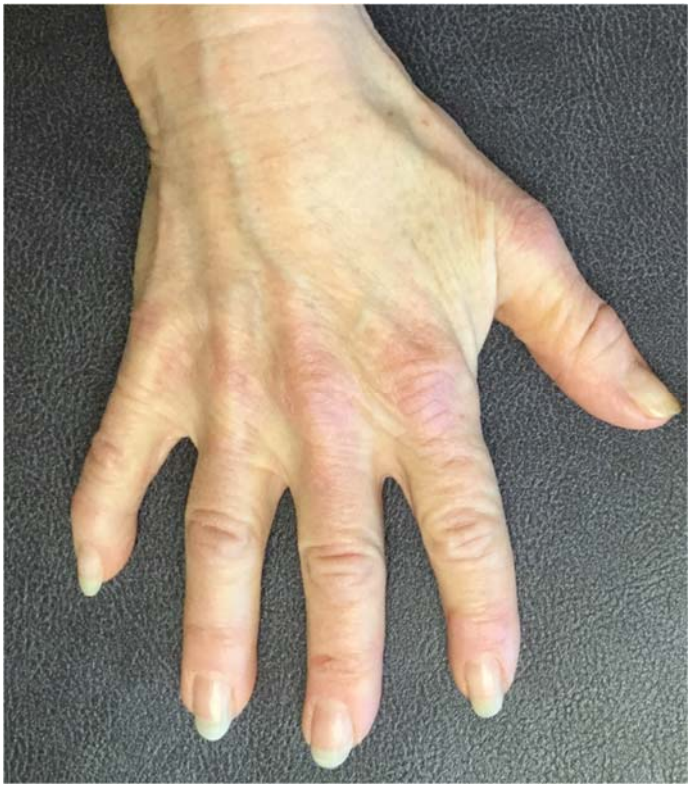

Figure 3. *Resolution of lesions on dorsal hands two months following resection of the pancreatic neuroendocrine tumor.*

with a number of autoantibodies including the various aminoacyl tRNA synthetases (Jo-1, OJ, EJ, PL-7, and PL-12), Mi-2, NXP-2, SRP, and TIF1γ antibodies [4].

Transcriptional intermediary factor 1γ belongs to the tripartite motif (TRIM) family of proteins that normally play a role in regulation of transcription. DM patients with the TIF1γ autoantibody (anti-p155, anti-p155/140) have significantly higher rates of malignancy than those without it [4, 5]. In addition to the increased risk for malignancy, patients with the TIF1γ autoantibody may also have more extensive cutaneous manifestations and unique clinical characteristics compared to those without it. Patients with the TIF1γ autoantibody are more likely to be female and have hyperkeratotic lesions, diffuse photoerythema, and "red on white" poikiloderma. They are less likely to have Raynaud phenomenon and arthralgias. These patients also have lower levels of muscle enzymes (CK, aldolase) and are more likely to be amyopathic compared to DM patients without the autoantibody [7].

Very few reports of dermatomyositis associated with neuroendocrine tumors have been reported in the literature. There have been several reports of lung and liver NETs associated with DM. However, in these cases the tumors were malignant [8–10]. There is one previously reported case of DM associated with a benign pancreatic neuroendocrine tumor (PNET), [6]. The patient in this case presented with DM two years following discovery of a 4cm PNET. This is in contrast to our case, in which dermatomyositis was the first sign of the underlying PNET. Additionally, the previous case report did not indicate the presence of TIF1γ autoantibodies. Both cases required surgical removal of the PNET with significant improvements in symptoms and in our case, improvement in the TIF1γ autoantibody levels. A previously reported case series described only 2 of 17 patients with TIF1γ autoantibody-positive cancer associated myositis becoming negative for the autoantibody following treatment for the underlying malignancy [11].

Current guidelines and evidence support active surveillance of non-functional PNETs that are less than 2cm [12,13]. Our case, along with the previously described case report, supports the surgical removal of non-functional PNETs in patients with DM refractory to medical treatment.

Conclusion

The association between malignant neoplasms and TIF1γ antibody positive DM is well established. However, the link between TIF1γ autoantibodies and benign neoplasms has not been previously described. Our case highlights that benign neoplasms as well as malignancy may be associated with the TIF1γ autoantibody and that patients with DM associated PNETs may benefit from excision. Interestingly, our patient also had a reduction in TIF1γ autoantibody levels following removal of the PNET. This may suggest that TIF1γ autoantibody levels may parallel the clinical course of DM. Further research in this area is warranted.

Potential conflicts of interest

The authors declare no conflicts of interests.

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