A case of dermatomyositis with underlying unusual malignancy

Sir,

Dermatomyositis is a rare autoimmune idiopathic inflammatory myositis with an incidence of about 1/100,000 population.1 Peri-orbital edema is commonly seen in patients with dermatomyositis, while with severe inflammatory involvement, edema can also be seen at other sites such as limbs and trunk. Rarely, anasarca may be the presenting manifestation of dermatomyositis. Various theories proposed for the pathogenesis of subcutaneous edema include the immune complex-mediated vasculitis, complement activation and vascular endothelial damage, leading to increased vascular permeability and edema in the tissues and muscles.2 Subcutaneous edema is also considered by some to be a marker of very active inflammation suggesting a poor prognosis. A search of the literature yielded about twenty cases reported previously where patients

1. Perrin C. Tumors of the nail unit. A review. Part II: Acquired lesions. J Am Acad Dermatol 1989;20:798-815.
2. Fanti PA, Tosti A. Subungual epidermoid inclusions: Report of 8 cases. Dermatologica 1989;178:209-12.
3. Wang BY, Eisler J, Springfield D, Klein MJ. Intraosseous epidermoid cyst discovered in the distal phalanx of a thumb: A case report. Hand Surg 2004;9:399-402.
4. Shin JJ, Kwon KY, Oh JR. Intraosseous epidermoid inclusion cyst in a great toe. A case report and review of the literature. Arch Pathol Lab Med 2003;127:e298-300.
5. Basak T. Unusual localization of multiple myxoid (mucous) cysts of the periarticular extensor tendon. Dermatol Venereol Leprol 2007;33:120-3.
6. Bukhari IA, Al-Mugharbel R. Subungual epidermoid inclusions. Saudi Med J 2004;25:522-3.
7. de Berker D, Goettman S, Baran R. Subungual myxoid cysts: clinicopathological correlation. Arch Dermatol 1986;122:1288-91.
8. Kivanc-Altunay I, Kumbasar E, Gokdemir G, Koslu A, Tekkesin M, Gevrek C. Fistulizing subungual epidermoid inclusion cyst. Int J Dermatol 2002;41:306-7.
9. Berger TG, Issa A, Stone EA. Subungual epidermoid inclusion cysts. J Am Acad Dermatol 2007;56:336-9.
10. Kouri NA, El-Hamamsy MA, Ahmed AG, El-Tahawy AH. Subungual epidermoid inclusions: A rare presentation of a rare entity. J Egypt Acad Dermatol 2015;57:199-201.
presenting with anasarca rapidly developed other features of dermatomyositis. Out of these, only five cases had an underlying carcinoma (endometrial, prostate, colon, gastric and cervical).

We report the case of a 55-year-old woman, who presented to the casualty with generalized edema for 2 months. This was followed by marked peri-orbital edema and itchy red lesions on the face, neck, chest, shoulders, thighs and buttocks. Though initially there was no muscle weakness, within 2 weeks, she developed rapidly worsening proximal muscle weakness of both the upper and lower extremities. On physical examination, there was peri-orbital edema along with pedal edema [Figure 1]. Cutaneous examination showed the presence of macular violaceous erythema over the peri-orbital area (heliotrope rash), forehead, nasolabial folds, pinnae, V area of the chest (shawl sign), left shoulder, buttocks, thighs (holster sign), elbows and knees (Gottron’s sign) [Figure 2]. There were no Gottron papules. Serum creatine phosphokinase (634 U/L [50–200]) and lactate dehydrogenase (1954 U/L [220–600]) were elevated. Muscle biopsy from the triceps showed chronic inflammatory infiltrate between the muscle fibers. Skin biopsy from erythematous plaque showed interface dermatitis with perivascular and peri-follicular inflammatory infiltrate and abundant mucin deposition in the dermis. Lesional direct immunofluorescence showed linear positivity of immunoglobulin G (2+) and C3 (1+) along the dermoepidermal junction. On indirect immunofluorescence, antinuclear antibody was positive in a diffuse pattern (3+), anti-double-stranded DNA antibody (dsDNA) was positive (2+, 100 IU/ml) and anti-Jo-1 antibodies were negative. Ultrasound abdomen revealed cholelithiasis with a polypoidal iso to hypo-echoic lesion adherent to the posterior wall of the gall bladder of suspected malignant etiology. Further evaluation by a contrast-enhanced computed tomography thorax, abdomen and pelvis showed cholelithiasis with enhancing soft tissue lesion (size 20x11mm) at fundo-posterior wall of gallbladder likely to be of malignant etiology. Hematological and biochemical investigations revealed raised erythrocyte sedimentation rate (70 mm in the 1st hour) and positive C-reactive protein with hypoalbuminemia (2.8 mg/dl, [normal 3.5–5 mg/dl]). Based on the above findings, a presumptive diagnosis of dermatomyositis with gallbladder malignancy was made.

Paraneoplastic dermatomyositis accounts for 15%–30% of all the cases of dermatomyositis, and it may precede (40%), develop concomitantly (26%) or follow (34%) the diagnosis of the malignancy. Most commonly associated malignancies are ovarian, bronchogenic, colorectal, gastric, non-Hodgkins lymphoma, breast, cervical, pancreatic, esophageal, bladder and renal malignancies. It has been hypothesized that the malignant cells express certain cryptic antigens on their cell surface, generating autoantibodies which cross react with the muscle cells to cause myositis. The risk factors for associated malignancy are old age, male sex, smoking, cutaneous leukocytoclastic vasculitis, cutaneous necrosis, lesions resistant to therapy, a rapid onset of myositis, dysphagia, raised erythrocyte sedimentation rate, C-reactive protein, raised creatine kinase, positive anti-transcription intermediary factor 1y, positive human leukocyte antigen-A28 and negative anti-Jo-1. Gallbladder malignancy is extremely rare with dermatomyositis. To the best of our knowledge, only eight such cases have been reported till date which are illustrated in Table 1. In all the previously reported cases, the malignancy was found after the diagnosis of dermatomyositis was made, as seen in our case.
Table 1: Previously reported cases of diabetes mellitus with gallbladder malignancy

| Authors                      | Year | Age/sex | Place            | Clinical sites                        | Muscle involved          | Treatment                              | Follow-up                                      |
|------------------------------|------|---------|------------------|---------------------------------------|--------------------------|----------------------------------------|-----------------------------------------------|
| Yiannopoulos et al.¹         | 2002 | 75/female | The Netherlands  | Heliotrope rash, Gottron’s papules   | Proximal muscles, neck    | Steroids, inoperable at exploratory laparotomy | Metastasis, lower lobe pneumonia, death       |
| Kundu et al.¹                | 2005 | 44/male  | India            | Proximal muscles                      | Proximal muscles         | Steroids                               | Lost to follow-up                             |
| Narasimhaiah et al.³         | 2011 | 65/female | India            | Proximal muscles                      | Proximal muscles         | Death before operation                  | Death                                         |
| Ni et al.⁹                   | 2013 | 67/female | India            | Heliotrope rash, Gottron’s sign       | Proximal muscles         | Resection of gallbladder                | Resolution                                    |
| Sawada et al.¹⁰              | 2014 | 90/female | Japan            | Heliotrope rash, Gottron’s papules    | Steroids                 | Palliative care                         | Acute renal failure, death                    |
| Park et al.¹¹                | 2014 | 71/male  | Korea            | Heliotrope rash, Gottron’s papules/sign | Proximal muscles         | Steroids, chemotherapy, inoperable cancer | Regular follow-up                             |
| Premkumar et al.¹²           | 2015 | 47/female | India            | Heliotrope rash, Gottron’s papules/sign | Stiffness, dysphagia     | Steroid, gemcitabine, cisplatin         | Palliative care, status same                  |
| Juricic¹³                    |      |         | Croatia          | Face, neck, ear                       | Proximal muscles         | Steroids, gemcitabine, cisplatin        |                                               |

Adenocarcinoma gallbladder stage T1b Nx [Figure 3]. With this treatment, the patient’s muscle weakness improved clinically and skin lesions started regressing. The patient was also started on oral methotrexate 7.5 mg weekly.

This case illustrates an unusual malignant association with dermatomyositis and highlights the importance of increased suspicion and heightened screening for malignant disease in elderly patients with dermatomyositis.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Tarun Garg, Sarita Sanke, Ram Chander, Mahima Agarwal, Kiran Agarwal, Ashok Kumar

Departments of Dermatology, Pathology and Surgery, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.

Correspondence: Dr. Sarita Sanke, Department of Dermatology and STD, Lady Hardinge Medical College, Shaheed Bhagat Singh Marg, New Delhi - 110 001, India. E-mail: sankesarita@gmail.com

References
1. Haroon M, Eltahir A, Harney S. Generalized subcutaneous edema as a rare manifestation of dermatomyositis: Clinical lesson from a rare feature. J Clin Rheumatol 2011;17:135-7.
2. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003;362:971-82.
3. Milisenda JC, Doti PI, Prieto-González S, Grau JM. Dermatomyositis presenting with severe subcutaneous edema: Five additional cases and review of the literature. Semin Arthritis Rheum 2014;44:228-33.
4. Callen JP. The value of malignancy evaluation in patients with dermatomyositis. J Am Acad Dermatol 1982;6:253-9.
5. Zhang W, Jiang SP, Huang L. Dermatomyositis and malignancy: A retrospective study of 115 cases. Eur Rev Med Pharmacol Sci 2009;13:77-80.
6. Yiannopoulos G, Ravazoula P, Meimaris N, Stavropoulos M, Andonopoulos AP. Dermatomyositis in a patient with adenocarcinoma of the gall bladder. Ann Rheum Dis 2002;61:663-4.
7. Kundu AK, Karmakar PS, Bera AB, Pal SK. Carcinoma of the gall bladder presenting as dermatomyositis. J Assoc Physicians India 2005;53:219-22.
8. Narasimhaiah DA, Premkumar JA, Moses V, Chacko G. Carcinoma of gall bladder presenting as dermatomyositis. Ann Indian Acad Neurol 2011;14:44-6.
9. Ni QF, Liu GQ, Pu LY, Kong LI, Kong LB. Dermatomyositis associated with gallbladder carcinoma: A case report. World J Hepatol 2013;5:230-3.
10. Sawada T, Nakai N, Masuda K, Katoh N. Paraneoplastic dermatomyositis associated with gallbladder carcinoma: A case report and mini-review of the published work. Indian J Dermatol 2014;59:615-6.
11. Park JS, Pyo JY, Park YB, Lee SK, Lee SW. Dermatomyositis associated with gallbladder cancer. J Rheum Dis 2014;21:261-5.
12. Premkumar M, Vyas T, Vashistha C, Kumar C, Rastogi A, Sharma P. Gall bladder adenocarcinoma masquerading as dermatomyositis. Oncol Gastroenterol Hepatol Rep 2014;3 Suppl S1:32-5.
13. Juricic P. Dermatomyositis as the first manifestation of gallbladder adenocarcinoma: Case report and literature overview. World J Surg Oncol 2015;13:127.
Ectodermal dysplasia-skin fragility syndrome (EDDFS) was first described by McGrath et al. in 1997. Ectodermal dysplasia-skin fragility syndrome is a rare inherited syndrome that occurs as a result of mutation in the PKP 1 gene, and is characterized by palmoplantar keratoderma, hypohidrosis, and brittle hair. Some characteristics of this condition include chronic diarrhea and congenital megacolon, as well as keratoses and painful fissures.

In our case, a 29-year-old male patient was admitted with complaints of trauma are specific findings of epidermolysis bullosa (EB) disease. Ectodermal dysplasia-skin fragility syndrome is characterized by PKP 1 mutation, which results in the autosomal recessive genodermatosis that is recently defined. In our case, there were palmoplantar keratoderma with erosions of the skin, brittle hair and nail dystrophy. EDDFS may occur as a result of mutation in the PKP 1 gene, and is characterized by the loss of function mutations of this gene which result in changes in PKP 1 protein levels.

We performed DNA sequencing analysis which detected a novel heterozygous p.Val472Glyfs*28 (c.1414_1415delTG) mutation in our index case, and in the father and mother of the case. This mutation, which has not been previously reported, leads to premature protein termination. Two bioinformatics tools - PolyPhen-2 and Mutation Taster, predict the p.Val472Glyfs*28 (c.1414_1415delTG) mutation to be “probably damaging”, and “disease causing”, respectively [2,5-12].

In literature, we could find about three brothers were asymptomatic. His parents were second-degree relatives and his sister reportedly died at the age of 5 years with similar complaints. His parents and sister had no related complaints. Therefore, this syndrome is classified as a specific suprabasal form of EB simplex at the IIIrd International Consensus Meeting for the diagnosis and classification of EB.

Hypohidrosis has been reported in a 40-year-old Japanese patient and a 20-year-old male Turkish patient. Dystrophic changes in the nail are also frequent findings. Keratoderma is common. Alopecia or thinning hair which is dry, short and curly is the typical appearance. Dystrophic changes in the nail occur as a result of mutation in the PKP 1 gene, and is characterized by the PKP1 protein is encoded by widespread skin fragility, alopecia, nail dystrophy, palmoplantar keratoderma and painful fissures.

In our index case, the patient had a homozygous splice site mutation (1233–2 A→T; c.369–2 A→T) detected by the PKP1 sequencing analysis. In our index case, we found a homozygous splice site mutation that has not been previously reported. The mutation changes the codon for valine to glycine and causes a premature stop codon (p.Val472Glyfs*28). This mutation was found in the father and mother of the case. Two bioinformatics tools - PolyPhen-2 and Mutation Taster, predict the p.Val472Glyfs*28 mutation to be “probably damaging”, and “disease causing”, respectively [2,5-12].

Histopathological examination revealed diffuse parakeratosis, prominent granular layer, submucosal cleavage between the keratinocytes. In the focal area and increased intercellular edema between the keratinocytes. The patient had a normal scalp, but his hair appeared short, and his hair was dry and brittle. His nails were also dystrophic. His parents and siblings had no related complaints.

In summary, Ectodermal dysplasia-skin fragility syndrome is a rare inherited syndrome that occurs as a result of mutation in the PKP 1 gene. The mutation leads to premature protein termination and results in the autosomal recessive genodermatosis that is characterized by palmoplantar keratoderma, hypohidrosis, and brittle hair. The mutation is predicted to be “probably damaging”, and “disease causing”.