Pyoderma Gangrenosum—A New Manifestation of Wilson Disease?

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Seventeen year old girl, a known case of Wilson disease presented to us with a non-healing skin ulcer followed by appearance of jaundice, ascites and progressive fatigue of 1 month duration. She was diagnosed to have Wilson disease 5 years back and had been well controlled on D-penicillamine. On enquiry, she was found to be noncompliant with her medication in the preceding 6 months. On examination, she had severe pallor, icterus with moderate ascites and oedema feet. Investigations revealed severe haemolytic anemia and deranged liver function. The lesion was diagnosed to be pyoderma gangrenosum on skin biopsy. The appearance of a cutaneous lesion followed by deterioration in the liver disease and hemolysis suggested uncontrolled Wilson disease as the triggering factor. Chelation therapy improved her haemoglobin and liver function as well as led to healing of the ulcer. We describe pyoderma gangrenosum as a new manifestation of Wilson disease. (J CLIN EXP HEPATOL 2016;6:62–64)

Extra hepatic manifestation of Wilson disease is rare. Dermatological manifestations are more often seen as a result of treatment. We describe the case of a 17 year girl, who developed pyoderma gangrenosum, which is usually described with inflammatory bowel disease and not described so far in the setting of Wilson disease.

CASE

A 17-year-old girl, born out of non-consanguineous marriage, was apparently alright until a month prior to the presentation. She had developed pustules over left calf, which broke down to form a non-healing raw area. Local treatment of the ulcer had not helped. This was followed 2 weeks later by fatigue, weakness and yellowish discoloration of eyes. She was a known case of Wilson disease since the last 5 years and was well controlled on D-penicillamine. On enquiry, she revealed that she was non-compliant with medications since the last 6 months. She had presented 5 years prior with liver dysfunction and ascites, which on investigations was proven to be Wilson disease. [Serum ceruloplasmin 4 mcg/dl, presence of K-F rings on slit lamp examination, 24 h urine copper 285 µg and liver copper of 315 µg dry weight of liver.] She neither had any

neurological symptoms nor any family history of a similar disease. On examination, the girl was well oriented in time, place and person. She had tachycardia, severe pallor, icterus, oedema feet and moderate ascites with a 3 cm palpable spleen. On cutaneous examination, there was an evidence of 2 skin ulcers, measuring 3 cm × 4 cm and the other one was about 4 cm × 5 cm. The floor of the ulcer was covered with necrotic slough, the edges had undermined margins were rolled up and the base of the ulcer was soft (Figure 1a and b). On palpation, there was bleeding from the ulcer.

The direct Coomb's test was negative. The antinuclear antibody was positive at a titre of 1:100, anti-Ds DNA and antihistone antibodies were negative. A stool analysis for occult blood was negative and colonoscopy ruled out the presence of inflammatory bowel disease. A biopsy of the skin lesion (Figure 2) was taken and it showed moderate superficial perivascular mixed infiltrate of lymphocytes and neutrophils with mild focal spongiosis. The epidermis showed infiltration by neutrophils in areas of spongiosis. There were no blisters or acantholysis. This was consistent with pyoderma gangrenosum which is a type of neutrophilic dermatosis.

The patient was started on regular chelation therapy with trientine of 1 g daily in divided doses. She was also treated with diuretics, salt restriction, high protein and low copper diet. She was given packed red cell transfusions.

Local treatment for skin ulcer was continued by cleaning the ulcer regularly with normal saline and betadine and debriding of the necrotic tissue. Local application with fusidic acid on the ulcer and halobetasol propionate cream (0.05%) surrounding the ulcer was done. The ulcer started improving with formation of granulation tissue. The depth of the ulcer reduced and became a superficial ulcer

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Abbreviations: ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; Ds-DNA: double stranded-deoxyribo nucleic acid; K-F: rings Kayser–Fleischer rings; WBCs: white blood cells

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Figure 1 (a) Two pustules which have ruptured and oozing blood. (b) Coalescing of 2 ulcers to form a large ulcerated area covered with necrotic slough and oozing blood.

Figure 2 H and E stain—showing superficial perivascular neutrophils and lymphocytes.

over a period of 2 months (Figure 3). No new lesions were found. Her liver function also gradually improved (Table 1) and the oedema feet and abdominal distension resolved.

Pyoderma gangrenosum is a rare disease, and it is a type of neutrophilic dermatosis.¹ The peak incidence occurs between the ages of 20–50 years with a possible slight female preponderance, and approximately 4% of patients are children.² Immunological factors and neutrophil dysfunction can be considered to be involved in etiopathogenesis of pyoderma gangrenosum.¹ The predisposed patient experiences an inciting event such as minor trauma, and instead of normal response that recognises and removes the damaged tissue, the patient's abnormal response results in the typical lesions of the disease. *Ulcerative (classic form)* is the most common type of pyoderma gangrenosum and the salient feature is a necrotic and mucopurulent tender ulcer with an oedematous, violaceous, serpiginously expanding, undermined border as was seen in our patient. It usually appears on the lower limb and the trunk but may occur at any site. The other variants are the bullous, vegetative and pustular forms.^{1,3}

Figure 3 Showing two healed ulcer covered with depigmented atrophic skin surrounded by peripheral hyperpigmentation.

The clinical course follows two patterns, our patient had indolent and gradually progressive type while the other type is explosive onset and rapidly progressive.

Pyoderma gangrenosum is the second more frequent and most debilitating cutaneous extra intestinal manifestation of inflammatory bowel disease patient.³ Our patient did not have symptoms of inflammatory bowel disease and the colonoscopy was normal. Pyoderma gangrenosum can also arise as a consequence of drug therapy like propylthiouracil, pegfilgrastim (granulocyte stimulating factor), gefinib (epidermal growth factor receptor inhibitor), and isotretinoin.^{4,5} In our patient, the D-penicillamine was unlikely to be the trigger as patient was not on the drug. In fact, the inadequate decoppering due to stopping of D-penicillamine seemed to be the trigger. D-penicillamine by itself has been described to cause skin lesions like elastosis perforans serpiginosa in patients with Wilson disease when given over long period of time but this was clearly

Table 1 The Investigations, at 9 Months Prior to Presentation when Patient was Clinically Well on Admission and 2 Months After Chelation, Have Been Tabulated.

	Normal range	9 Months prior	On admission	2 months after chelation
Haemoglobin (g/dl)	13–18	11.5	4.9	12.4
White blood cells (/cmm)	4000–10000	6400	9490	6200
Platelets (/cmm)	140000–440000	150,000	130,000	116,000
Total bilirubin (mg/dl)	0.2–1.3	1.7	6.7	3.1
Direct bilirubin (mg/dl)	0.1–0.8	1.1	3.2	2.1
Aspartate aminotransferase (IU/L)	5–40	56	367	121
Alanine aminotransferase (IU/L)	10–40	48	406	74
Alkaline phosphatase (IU/L)	30–150	280	371	210
Total protein (g/dl)	6.3–8.2	6.5	6	6.1
Serum albumin (g/dl)	3.5–5.0	3.2	2	2.4
24 h urine copper (µg)	0–75	320	42	351
International normalized ratio	1.0	1.4	2.3	1.3
Reticulocyte count (%)	0–2.0%	–	8.2	0.9

not that.⁶ In 1976, two cases of pyoderma gangrenosum associated with chronic active hepatitis were reported, although the aetiology of hepatitis was not known.⁷ These patients may have had Wilson disease. Pyoderma gangrenosum can also be associated with other underlying conditions like seropositive rheumatoid arthritis, myeloproliferative disorders and vasculitis,⁸ which were not the possible causes in our case.

The Coombs negative haemolytic anaemia, the decompensation of liver function and simultaneous occurrence of the skin lesions coincided with the discontinuation of D-penicillamine. Also the resolution of the skin ulcers and improvement in liver function after restarting chelation supported the fact that uncontrolled Wilson disease was the likely cause of the skin ulcers.

An association between the skin and the liver disease has been recognised since ancient times. Chronic liver disease can give rise to numerous extrahepatic disorders, among which dermatological diseases occupy a central place and at times point to aetiology of disease.

Hepatobiliary disease can cause cutaneous manifestations in several ways, liver disease may cause skin changes. Skin and liver may be involved by the same pathologic process, skin disease may cause liver abnormalities and liver may be damaged by drugs used to treat skin diseases.⁹ The clinical signs of chronic liver disease mentioned in medical literature are spider naevi, clubbing, leuconychia, palmar erythema, Dupuytren's contracture, loss of axillary hair, testicular atrophy, gynaecomastia, jaundice and ascites.¹⁰ Unusual skin lesions often signify a systemic problem and should not be overlooked. In this report, we add

pyoderma gangrenosum as another skin disease associated with a liver disease i.e., Wilson disease.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Bhat RM, Nandakishore B, Sequeira FF, et al. Pyoderma gangrenosum: an Indian perspective. *Clin Exp Dermatol*. 2011;36:242–247.
2. Powell FC, Su WP, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol*. 1996;34:395–409.
3. Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol*. 2009;23:1008–1017.
4. Wollina U. Pyoderma gangrenosum: a review. *Orphanet J Rare Dis*. 2007;2:19.
5. Tinoco MP, Tamler C, Maciel G, et al. Pyoderma gangrenosum following isotretinoin therapy for acne nodulocystic. *Int J Dermatol*. 2008;47:953–956.
6. Atzori L, Pinna AL, Pau M, Aste N. D-Penicillamine elastosis perforans serpiginosa: description of two cases and review of the literature. *Dermatol Online J*. 2011;17(4):3.
7. Byrne J, Summerly R. Pyoderma gangrenosum associated with active chronic Hepatitis: reports of two cases. *Arch Dermatol*. 1976;112:1297–1301.
8. Bhat RM. Pyoderma gangrenosum—an update. *Indian Dermatol Online J*. 2012;3:7–13.
9. Khan MM, Noor SM, Rehman S, et al. Cutaneous manifestation of chronic liver disease. *J Pak Assoc Dermatol*. 2005;15:233–237.
10. Ogilvie C, Cristopher C, Evans CC. *Chamberlains Symptoms & Signs in Clinical Medicine*. 12th ed. Butterworth Heinemann; 1997: 78–81.