Erythropoietin induced miliaria crystallina: A possible new adverse effect of erythropoietin

Sumir Kumar, B.B. Mahajan, Sandeep Kaur, Amarbir Singh

ABSTRACT

Introduction: Erythropoietin, also known as EPO, is used for the treatment of anemia of chronic kidney disease. Usually, the drug is well tolerated with only a few side effects. Adverse effects are mostly systemic with hypertension being seen frequently. Various cutaneous side effects include pruritus, rash, urticaria and erythema. However, miliaria induced by erythropoietin has not been reported so far.

Case Report: A 74-year-old female was referred from medicine department with possibility of toxic epidermal necrolysis. She developed crops of non-itchy tiny vesicles filled with clear fluid on body for the last three days. Injection erythropoietin was given six hours prior to onset of rash. Similar episode occurred one week back after the use of erythropoietin. There was no history of any acute febrile illness. She was a known case of hypertension, diabetes mellitus with chronic kidney disease. There was no change in the treatment plan for the above mentioned complaints except introduction of erythropoietin recently for the management of severe anemia secondary to chronic kidney disease. The diagnosis of miliaria crystallina was made clinically and spontaneous resolution occurred in about seven days.

Conclusion: This case adds erythropoietin among the list of drugs precipitating miliaria crystallina which is being reported for the first time in literature. Recognizing this otherwise benign clinical entity is important as it can be confused with severe drug reactions such as toxic epidermal necrolysis. The absence of inflammatory signs in skin, lack of mucosal involvement, no systemic manifestations and spontaneous resolution can help to distinguish it from other drug reactions.

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CASE REPORT

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Introduction: Erythropoietin, also known as EPO, is used for the treatment of anemia of chronic kidney disease. Usually, the drug is well tolerated with only a few side effects. Adverse effects are mostly systemic with hypertension being seen frequently. Various cutaneous side effects include pruritus, rash, urticaria and erythema. However, miliaria induced by erythropoietin has not been reported so far. **Case Report:** A 74-year-old female was referred from medicine department with possibility of toxic epidermal necrolysis. She developed crops of non-itchy tiny vesicles filled with clear fluid on body for the last three days. Injection erythropoietin was given six hours prior to onset of rash. Similar episode occurred one week back after the use of erythropoietin. There was no history of any acute febrile illness. She was a known case of hypertension, diabetes mellitus with chronic kidney disease. There was

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Keywords: Erythropoietin, EPO, Miliaria, Eccrine sweat glands

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INTRODUCTION

Erythropoietin (EPO) is a glycoprotein that controls erythropoiesis. It is used frequently for the treatment of anemia of chronic kidney disease. Its adverse effects are mostly systemic with hypertension being seen frequently. We report a case of a 74-year-old female who got referred to us with possibility of toxic epidermal necrolysis. Subsequently, diagnosis of miliaria induced by EPO was established and patient recovered spontaneously. This side effect has not been reported so far. This case report,

thus, highlights this unrecognized adverse effect and importance of differentiating it from other serious drug reactions.

CASE REPORT

A 74-year-old female was referred to us from medicine department with possibility of toxic epidermal necrolysis. She complained of development of crops of non-itchy tiny vesicles filled with clear fluid on body for last three days. Injection EPO was given six hours prior to onset of rash. Similar episode occurred one week back after the use of EPO. There was no history of any acute febrile illness. She was a known case of hypertension, diabetes mellitus with chronic kidney disease. There was no change in the treatment plan for the above mentioned complaints except introduction of EPO recently for management of severe anemia secondary to chronic kidney disease.

Physical examination revealed afebrile patient with blood pressure 160/90 mmHg. On local examination, multiple, discrete, fragile vesicles filled with clear fluid on normal appearing, non-tender skin were evident in left inframammary area along with branny desquamation on the back, abdomen and thighs, buttocks (Figure 1A–B). Rest of the body including palms, soles and mucosae was normal. Laboratory results of the patient revealed hemoglobin 5 g/dL, with microcytic and normocytic anemia, serum creatinine 3.5 mg/dL, blood urea 50 mg/dL, clotting time 8 minutes (normal 2–6 minutes), prothrombin time 20 seconds (normal 11–15 seconds). Liver function tests and electrolytes were within normal limits. Viral markers were non-reactive. Biopsy was not done in view of severe anemia, deranged coagulation profile, immunosuppressed state of CRF and clear distinct clinical picture.

The diagnosis of miliaria crystallina was made clinically. She was managed conservatively tab hydroxyzine 10 mg HS, tab ranitidine 150 mg BD, calamine lotion for local application BD. She improved in about seven days without any sequelae (Figure 1C–D).

DISCUSSION

Eccrine sweat glands are a type of sweat glands that are distributed widely over the body surface and produce hypotonic sweat. The evaporation of sweat helps in thermoregulation through the loss of extra heat. Activity of these glands is controlled by the thermoregulatory centre located in preoptic region of the hypothalamus. Innervation occurs through the sympathetic post ganglionic fibres arising at the spinal cord thoracic and lumbar regions T1–L2. In contrast to ordinary sympathetic innervation, acetylcholine is the principle neurotransmitter. Although it also has an adrenergic component. Sweat cells exhibit cholinergic and alpha and beta adrenergic receptors on their basolateral membrane.

Thus, both adrenergic and cholinergic stimulation results in increased sweating. There is also role of intracellular calcium in acetylcholine mediated stimulation of eccrine sweating (Figure 2).

It is the obstruction or disruption of these eccrine glands that results in miliaria [1]. The three forms of miliaria, miliaria crystallina, miliaria rubra (prickly heat) and miliaria profunda, differ in clinical form due to the different levels at which obliteration occurs, with pathology being present at the level of stratum corneum, intraepidermal and at or below the dermal-epidermal junction, respectively.

Miliaria crystallina is seen in conditions associated with profuse sweating and high humidity. It occurs commonly in infants due to a delay in patency developing

Figure 1: (A) Desquamation on trunk with background skin being normal at the time of presentation, (B) Close-up view of vesicles: fragile vesicles filled with clear fluid without any signs of inflammation, (C) Normal looking skin on anterior trunk after resolution of miliaria, (D) Resolution of miliaria on posterior trunk.

Figure 2: The role of intracellular calcium in the production of eccrine sweat.

in the sweat ducts. It can also uncommonly occur in adults during episodes of febrile illnesses associated with profuse sweating. Profuse sweating results in overhydration of stratum corneum which results in obstruction of acrosyringium.

Recognizing this otherwise benign clinical entity is important as it can be confused with drug reactions such as toxic epidermal necrolysis. The absence of inflammatory changes in skin, and absence of systemic manifestations and spontaneous resolution can help to distinguish it from other drug reactions.

Erythropoietin is produced normally by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. Erythropoietin available for use as therapeutic agents is produced by recombinant DNA technology in cell culture. Its use is associated with some adverse effects with hypertension being reported in 20–30% patients treated for anemia of chronic kidney disease [2]. This side effect is less common with subcutaneous route as compared with intravenous administration [3, 4]. Various factors are thought to contribute to hypertension as exemplified in various studies [5–7]. Of these mechanisms like alpha adrenergic hyper-responsiveness and marked increase in intracellular calcium levels could possibly have contributed to the pathogenesis of miliaria in our patient. Other cutaneous side effects reported include pruritus, rash, urticaria (3%), erythema (1%).

When exogenous EPO is used as a performance-enhancing drug through the enhancement of oxygen delivery to muscles, it is classified as an erythropoiesis-stimulating agent (ESA) and has been used in various sports. Hence, it is included under category of doping agents.

There are several case reports of drug precipitated miliaria, but due to EPO they have not been reported so far. So this may be the first report of this unique side effect. Isotretinoin induces miliaria through the alteration of follicular differentiation [8]. Bethanechol, a drug that promotes sweating due to its parasympathomimetic effect, has been reported to cause miliaria, as have clonidine and neostigmine [9]. A single case of miliaria crystallina following doxorubicin administration has been reported, mechanism of which remains obscure [10].

CONCLUSION

This case adds erythropoietin (EPO) among the list of drugs precipitating miliaria crystallina which is being reported for the first time in literature. Recognizing this otherwise benign clinical entity is important as it can be confused with severe drug reactions such as toxic epidermal necrolysis. The absence of inflammatory signs in skin, lack of mucosal involvement, no systemic manifestations and spontaneous resolution can help to distinguish it from other drug reactions.

Author Contributions

Sumir Kumar – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

B.B. Mahajan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Sandeep Kaur – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Amarbir Singh – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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