Essential Thrombocythemia: The Dermatologic Point of View

Emanuele Cozzani,[1] Alessandra Iurlo,[2] Giulia Merlo,[1] Daniele Cattaneo,[3] Martina Burlando,[1] Ivana Pierri,[4] Luigi Gugliotta,[5] Aurora Parodi[1]

Abstract

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by an increase in blood platelets and dominated by a predisposition to vascular events. Cutaneous manifestations can complicate its course. itching has been the most common symptom reported; however, the percentage has ranged from 3% to 46%, depending on the survey. Erythromelalgia is found in 6% of cases, and livedo reticularis, minor bleeding, acrocyanosis, and Raynaud's phenomenon are rare manifestations. It is important to recognize and treat these events, because they can affect patients' quality of life and could worsen the prognosis. In addition to skin involvement as a possible sign of ET, the treatment of ET can be associated with cutaneous complications. Hydroxycarbamide, interferon-alfa, and anagrelide can induce different skin lesions. Hydroxycarbamide has been associated with major complications, including painful leg ulcers and actinic keratoses. Minor events include alopecia and hyperpigmentation. Xerosis, pruritus, and photosensitivity are some of the complications reported by patients treated with interferon-alfa. Anagrelide has proved to be associated with fewer dermatologic effects, only detected in single cases. Knowledge of the ET cutaneous manifestations, together with the clinical examination findings, can result in an earlier diagnosis and the start of effective treatment.

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Introduction

Essential thrombocythemia (ET) is a BCR-ABL1−negative myeloproliferative neoplasm (MPN) mainly characterized by an increase in megakaryocyte production with sustained thrombocytosis (> 450,000/mm^3).[1-4] The prevalence in the general population ranges from 11.00 to 42.5 per 100,000 (MPN Research Foundation).[5] The median age at diagnosis is 65 to 70 years; however, ET can occur at any age. The male-to-female ratio is about 1:2.

Currently, the diagnosis of ET should use the World Health Organization 2008 criteria, which is based on a composite assessment of clinical and laboratory features, among which molecular analyses play a crucial role.[4] In 2005, the *JAK2* V617F mutation was reported to be involved in the pathogenesis of these disorders and is identifiable in about 55% to 65% of patients with ET.[6-9] Subsequently, mutations somatically acquired in genes other than *JAK2* have been described, including in the *MPL* gene, with a frequency of 3% to 8%,[10,11] and, more recently, in the calreticulin (*CALR*) gene.[12,13] Although in these patients, overall survival is near normal and the 10-year risk of acute myeloid leukemia or post-ET myelofibrosis evolution is < 1%,[14-17] the risk of thrombosis is > 20%, and a substantial proportion of patients with ET experience vasomotor disturbances (eg, headaches, lightheadedness, acral paresthesia, erythromelalgia).[18] Therefore, the current treatment of ET should primarily prevent thrombohemorrhagic events, without increasing the risk of bleeding and, secondarily, should control the above-mentioned symptoms.

Cutaneous manifestations can complicate ET, but they can also represent a helpful guide to the diagnosis,[19] because they can be the presenting symptoms.[20] Dermatologic involvement can alter a patient's quality of life[21,22] but can be easily managed if promptly recognized and treated.

With the retrospective and prospective studies conducted in previous years, we have increased our knowledge about the dermatologic manifestations of ET. One of the largest studies

[1]Di. S. Sal. Section of Dermatology, IRCCS Azienda Ospedaliera Universitaria, San Martino-IST, Genoa, Italy
[2]Oncohematology Division, Oncohematology Unit of the Elderly, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy
[3]Oncohematology Division, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy
[4]Department of Hematology and Oncology, IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genoa, Italy
[5]Institute of Hematology "L. e A. Seragnoli", S. Orsola Malpighi University Hospital, Bologna, Italy

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Address for correspondence: Emanuele Cozzani, MD, PhD, Di. S. Sal. Section of Dermatology, IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Via Pastore 1, Genoa 16132, Italy
E-mail contact: emanuele.cozzani@unige.it

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aiming to describe the skin involvement with ET was conducted by Itin and Winkelmann[19] in 1991. Their study included 268 patients with ET and showed that 22% experienced dermatologic complications and 10% had cutaneous symptoms as the presenting sign of the disease. Furthermore, among the patients with dermatologic involvement, 28% had > 1 type of skin lesion.[19]

Smaller studies conducted by Michiels et al,[20] with 40 patients, and Hehlmann et al,[23] with a cohort of 61 patients, focused on specific dermatologic manifestations, such as erythromelalgia and acrocyanosis. The cutaneous manifestations associated with ET are various and different and include microcirculation abnormalities, such as erythromelalgia, acrocyanosis, hematoma, ecchymosis, petechiae, purpura, superficial thrombophlebitis, Raynaud's phenomenon, livedo reticularis, ulceration, and ischemic gangrene. Other dermatologic involvement includes pruritus, urticaria, and xerosis.

In addition to skin involvement as a possible sign of ET, the treatment of ET can be associated with cutaneous manifestations. The therapeutic options include the use of cytoreductive drugs, such as hydroxycarbamide (HC), interferon-alfa (IFN-alfa), and anagrelide. Almost 10% of 809 patients experienced a cutaneous adverse event in a large randomized trial of ET.[24] A variety of skin alterations, including leg and mouth ulcers, actinic keratoses (AKs), squamous cell carcinoma (SCC), alopecia, and nail changes, have mostly been associated with HC use.[25,26] Surveys of patients with ET treated with IFN-alfa have reported different adverse events, including xerosis, alopecia, itching, psoriasis, and necrosis. In contrast, anagrelide seems to be associated with only minor cutaneous adverse manifestations.

Knowledge of the drug-related cutaneous involvement could lead to earlier detection, appropriate management, and improvement in patients' quality of life. Our purpose was to perform a systematic review of the dermatologic manifestations of ET and drug-related skin complications to increase awareness of this disease and allow for earlier diagnosis and effective treatment.

Cutaneous Involvement as a Clinical Manifestation of ET

We report the main cutaneous manifestations described as presenting symptoms or possible complications in patients with ET to date.

Pruritus

The incidence of pruritus reported has varied among the different studies of patients with ET. In a survey of MPNs,[21] pruritus was reported in 40% of 304 patients with thrombocythemia. In another study of 594 patients with ET, 46% reported itching.[27] However, in the Thrombocythemia Italian Registry, drafted by Gugliotta and including data from 977 patients with ET, the rate of pruritus at diagnosis was only 3% (Gugliotta L, for the "Registro Italiano Trombocitemie" (RIT); personal communication, 2013).

The pathogenesis of pruritus in MPNs is that mast cells release greater amounts of histamine, leukotrienes, and interleukin-31 than is normal.[28] Itching often has a great effect on the quality of life of patients with ET.[22] Therefore, symptomatic management and education are important to reduce the incidence and severity of pruritus.[29] Patients should be advised to maintain a cool environment, eliminate tight clothing, and avoid topical irritant products and vasodilators, such as caffeine, alcohol, and hot water. If the problem persists, an alternative management option, such as phototherapy, should be evaluated. Narrowband ultraviolet (UV)B light 2 to 3 times a week in the initial regimen has been the most recommended choice. In addition, the application of topical products containing polidocanol or capsaicin ≥ 1 times daily can be helpful in relieving the symptoms.[22]

Erythromelalgia

Erythromelalgia is a rare condition that results in episodes of burning pain at the distal extremities and marked erythema, which is exacerbated by heat and exercise.[19] Most cases are idiopathic, although others occur secondary to medical conditions such as autoimmune diseases, neurologic disorders, and MPNs. Not many studies have been conducted on patients with ET. Erythromelalgia developed in 6% of 268 patients according to Itin and Winkelmann[19] and in 6% of 977 patients according to Gugliotta (Gugliotta L, for the RIT; personal communication). However, in a smaller study by Michiels et al,[20] the incidence was significantly different, with 26 of 40 patients (65%) reporting erythromelalgia.

Although the pathogenesis of erythromelalgia is not yet clear, it has been suggested that platelet thrombi and endothelial inflammation play a crucial role in its development, mainly through intravascular platelet activation and subsequent aggregation with occlusion of the arterioles. Histologically, erythromelalgia is associated with capillary proliferation, endothelial swelling, perivascular edema, and sparse lymphocytic infiltrates.[20]

The symptoms are episodic and can result in severe disability. Therefore, it is important to prevent and reduce this complication, because it can progress to necrosis of the fingers and toes.[30] Having patients rest, elevate their extremities, and expose their extremities to cold can be useful preventative measures.[31]

Therapy with full-dose acetylsalicylic acid (ASA) (500 mg/day, or more in some cases) can be required to alleviate pain. Partial symptom remission was also described with the use of sertraline (50 mg twice daily) and with some anticonvulsants such as gabapentin (300 mg, 1-3 times daily).[32] Among the available topical treatments, capsaicin cream, used ≥ 1 times daily, has been reported to alleviate erythromelalgia.

Acrocyanosis

Acrocyanosis, which is characterized by steadily cold and blue hands and feet,[33] represents a manifestation whose pathogenesis is still unknown. Itin and Winkelmann[19] identified this complication in only 4 of 268 patients. Wearing warm clothing and hygienic and alimentary education can reduce the incidence of acrocyanosis.[33]

Livedo Reticularis

Livedo reticularis is a rarer manifestation, described in only 3% of 268 patients with ET.[19] It consists of a persistent purplish network pattern change of the skin, similar to the familiar livedo reticularis, from which it differs by its location (which is more generalized and widespread, found not only on the limbs but also on the trunk) and its shape (irregular, broken, and circular segments).

Patients with ET who manifest livedo reticularis seem to do so with a limited extent and asymmetric distribution.[34] It has been thought that ET-related livedo reticularis mainly results from