

ORIGINAL ARTICLE

## Superficial Migratory Thrombophlebitis: A Clinical and Histologic Review of 8 Cases

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**Abstract.** *Introduction.* Superficial migratory thrombophlebitis (SMT) or thrombophlebitis migrans is characterized by recurrent episodes of localized thrombosis of the superficial veins in the limbs and trunk. It has been associated with various systemic diseases that should be taken into consideration when assessing the patient.

*Material and methods.* Between 1997 and 2007, 8 patients with SMT were seen at Hospital General Universitario de Valencia in Valencia, Spain. We review the clinical features and histopathology, along with the associated diseases.

*Results.* The most common clinical presentation was with painful nodules mimicking erythema nodosum on the lower extremities. Other sites were on the abdomen and trunk. Only in 1 case was SMT diagnosed clinically. In other cases, the clinical diagnoses were cellulitis, lymphangitis, nodular vasculitis, and panarteritis nodosa. The histologic characteristics were compatible with superficial thrombophlebitis, and orcein staining revealed the internal elastic lamina to be absent in all cases. No evidence of an occult tumor was found in any of the cases. Two cases had a history of Buerger disease and in another the condition presented in association with a fever of unknown origin.

*Conclusion.* The possible association of SMT with systemic diseases, including cancer, makes its diagnosis important. In our case series we did not find evidence of associated disease in the majority of cases. However, since cancer can manifest months and even years after the appearance of SMT, follow-up is necessary in these patients.

**Key words:** superficial migratory thrombophlebitis, thrombophlebitis migrans, Mondor disease, Trousseau sign.

### TROMBOFLEBITIS SUPERFICIAL MIGRATORIA: REVISIÓN CLÍNICA E HISTOLÓGICA DE 8 CASOS

**Resumen.** *Introducción.* La tromboflebitis superficial migratoria (TSM) o tromboflebitis *migrans* se caracteriza por episodios recurrentes de trombosis segmentaria de las venas superficiales de los miembros y el tronco. La TSM se ha asociado con diversas enfermedades sistémicas que deben tenerse en cuenta a la hora de evaluar al paciente.

*Material y métodos.* Desde 1997 hasta 2007, 8 pacientes con TSM fueron estudiados en el Hospital General Universitario de Valencia. Se revisaron las características clínicas e histopatológicas, así como las enfermedades asociadas.

*Resultados.* La presentación clínica más frecuente fue en forma de nódulos dolorosos recurrentes en las extremidades inferiores, similar a un eritema nodoso. Otras localizaciones fueron el abdomen y el tronco. Sólo en un caso el diagnóstico clínico fue de TSM. Otros diagnósticos clínicos fueron celulitis, linfangitis, vasculitis nodular o panarteritis nodosa. Las características histológicas fueron compatibles con tromboflebitis superficial, y

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la tinción con orceína mostró ausencia de la lámina elástica interna en todos los casos. En ninguno se demostró asociación con una neoplasia oculta. En 2 casos existían antecedentes de enfermedad de Buerger y otro apareció en el contexto de una fiebre de origen desconocido.

**Conclusión.** El reconocimiento de la TSM es importante por su posible asociación con enfermedades sistémicas, incluyendo el cáncer. En nuestra serie fuimos incapaces de encontrar una enfermedad asociada en la mayoría de los casos. Sin embargo, y dado que el cáncer se puede manifestar entre meses e incluso años después de la aparición de la TSM, es necesario el seguimiento de los pacientes.

**Palabras clave:** tromboflebitis superficial migratoria, tromboflebitis *migrans*, enfermedad de Mondor, signo de Trousseau.

## Introduction

Superficial migratory thrombophlebitis (SMT) or thrombophlebitis migrans is characterized by recurrent episodes of localized thrombosis of the superficial veins in the limbs and trunk. It has been associated with various systemic diseases that should be considered when examining the patient.

Here we describe a series of 8 patients seen by the Dermatology Department of Hospital General Universitario de Valencia, in Valencia, Spain, between 1997 and 2007.

## Materials and Methods

A search was undertaken to identify patients diagnosed with SMT in the Dermatology Department of Hospital

General Universitario de Valencia between January 1997 and April 2007.

The following data were routinely collected from the patient's medical history: age, sex, clinical presentation, clinical diagnosis, additional tests, and associated diseases. All biopsies were reassessed to analyze the characteristics of the epidermis, papillary dermis, type of infiltrate in the vascular wall, existence of organized thrombus, hemorrhage, and conditions of surrounding fat. Orcein staining was performed in all cases.

## Results

Tables 1 and 2 describe the results obtained from the search. Eight patients (5 men, 3 women) with a mean age of 52 years (range, 39-60) were identified. The most common clinical

**Table 1.** Epidemiological Data, Clinical Presentation, and Associated Diseases

Case	Sex/Age, y	Clinical Presentation	Clinical Diagnosis	Associated Diseases
1	M/60	Painful erythematous plaques on the legs	Periarthritis nodosa	Thromboangiitis obliterans
2	F/45	Recurrent infraumbilical erythematous nodules with a linear distribution	Superficial migratory thrombophlebitis	None
3	M/57	Hot erythematous plaques on right foot	Cellulitis	Peripheral venous insufficiency
4	M/47	Linear erythematous lesion on the chest wall	Lymphangitis	None
5	M/52	Painful recurrent nodules on the legs	Nodular vasculitis	Peripheral venous insufficiency
6	F/60	Painful pretibial plaque	Erythema nodosum	Fever of unknown origin Viral hepatitis C treated with interferon and ribavirin
7	F/39	Painful erythematous nodules with a linear distribution on the right leg	Erythema nodosum	No associated diseases
8	M/58	Painful erythematous nodules with a linear distribution on the right leg	Erythema nodosum	Thromboangiitis obliterans

Abbreviations: F, female; M, male.

**Table 2.** Histopathologic Features

	<i>Epidermis</i>	<i>Papillary Dermis</i>	<i>Infiltration of Vascular Wall</i>	<i>Organized Thrombus</i>	<i>Hemorrhage</i>	<i>Perivascular Infiltrate</i>	<i>Surrounding Fat</i>	<i>Orcein</i>
1	Atrophy	Proliferation of capillary vessels with thickened PAS+ basement membrane	Histiocytes Giant cells	–	–	Histiocytes Giant cells	Septal fibrosis	Absence of internal elastic lamina
2	Normal	Normal	Neutrophils Eosinophils Histiocytes	–	+	Histiocytes Eosinophils	Enderteritis obliterans Septal fibrosis	Absence of internal elastic lamina
3	Atrophy	Normal	Neutrophils Eosinophils Histiocytes	–	–	Histiocytes Eosinophils	Enderteritis obliterans Lipophagy	Absence of internal elastic lamina
4	Atrophy	Normal	Histiocytes Fibrosis	+ Minimal recanalization	–	Histiocytes	Fibrosis	Absence of internal elastic lamina
5	Normal	Proliferation of capillary vessels with thickened PAS+ basement membrane	Lymphocytes Histiocytes	+	+	Lymphocytes Histiocytes	Septal fibrosis	Absence of internal elastic lamina
6	Atrophy	Proliferation of capillary vessels with thickened PAS+ basement membrane	Lymphocytes Histiocytes Neutrophils	+	–	Lymphocytes Histiocytes	Enderteritis obliterans Septal fibrosis	Absence of internal elastic lamina
7a	Atrophy	Proliferation of capillary vessels with thickened PAS+ basement membrane	Neutrophils Eosinophils Histiocytes	–	–	Neutrophils Eosinophils Histiocytes	Enderteritis obliterans Mucin	Absence of internal elastic lamina
7b	Atrophy	Proliferation of capillary vessels with thickened PAS+ basement membrane	Eosinophils Histiocytes	+	–	Lymphocytes Histiocytes Eosinophils	Enderteritis obliterans Mucin	Absence of internal elastic lamina
8	Atrophy	Proliferation of capillary vessels with thickened PAS+ basement membrane	Histiocytes Lymphocytes Giant cells	+	–	Histiocytes Lymphocytes Giant cells	Enderteritis obliterans	Absence of internal elastic lamina

Abbreviation: PAS, periodic acid Schiff.

presentation was painful nodules in the legs (n = 6). Other sites were the abdominal region (n = 1) and trunk (n = 1). The various clinical diagnoses (Figures 1 and 2) were erythema nodosum (n = 3), nodular vasculitis (n = 1), periarteritis nodosa (n = 1), lymphangitis (n = 1), and cellulitis (n = 1). SMT was diagnosed clinically in only 1 case.

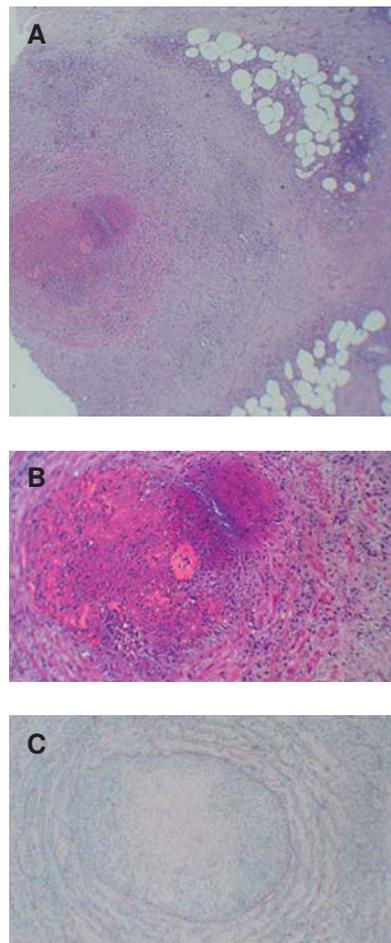
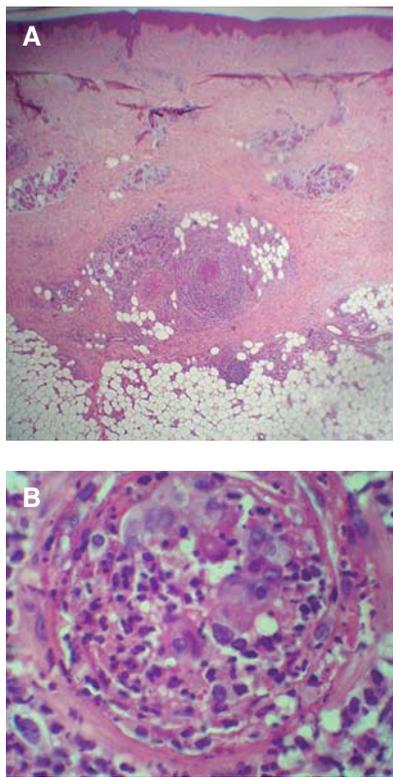
A total of 9 biopsies were carried out. In most, pathology showed epidermal atrophy (n = 7) and proliferation of the capillary vessels along with a thickened basement membrane that stained positive with periodic acid Schiff stain in the papillary dermis (n = 6). Ulceration was not observed in any patient.

**Figure 1.** Clinical presentation in patient 8. Erythematous nodules with a linear distribution on the right leg. The initial clinical diagnosis was erythema nodosum. This patient had a history of Buerger disease.



**Figure 2.** Clinical presentation in patient 3. Hot erythematous plaques on the left foot. The patient was initially diagnosed with cellulitis refractory to treatment with various antibiotics.

**Figure 3.** Histologic image from patient 7. A, Involvement of a large vein located in the superficial subcutaneous tissue (hematoxylin-eosin, #x40). B, Inflammatory infiltrates with neutrophils, eosinophils, and histiocytes throughout the entire vascular wall with occlusion of the lumen (hematoxylin-eosin, x400).



**Figure 4.** Histologic image from patient 8. A, Large vein in the superficial subcutaneous tissue with inflammation composed of histiocytes and giant cells and extending toward the surrounding fat (hematoxylin-eosin, x100). B, Organized thrombus occluding the vascular lumen (hematoxylin-eosin, x200). C, Orcein staining showed that the internal elastic lamina was absent (hematoxylin-eosin, x200).

All cases showed involvement of a large vein in the superficial subcutaneous tissue with occlusion of the vascular lumen (Figures 3 and 4). The inflammatory infiltrates in the vessel wall were composed of neutrophils (n = 4), eosinophils (n = 4), histiocytes (n = 9), lymphocytes (n = 3), and giant cells (n = 2). In addition, 5 biopsies showed an organized thrombus and 1 case had minimal

recanalization of the vascular lumen. Hemorrhaging was observed in 2 patients. The surrounding fatty tissue showed lipophagy (n = 1), proliferation of the capillary vessels and

endarteritis obliterans (n = 6), septal fibrosis (n = 5), and mucin (n = 2). In all cases, orcein staining confirmed the absence of the internal elastic lamina.

The mean time from the onset of symptoms until SMT diagnosis was 10 months (range, 1-24 months).

The extended study for each patient included a complete laboratory workup consisting of blood counts, biochemistry, autoimmunity, tumor markers, and a coagulation and thrombosis study, along with chest x-ray, and abdominal ultrasound. The patients were also assessed by a vascular surgeon. No evidence of an occult tumor (Trousseau sign) was seen in any patient. Patients 1 and 8 had a history of Buerger disease (thromboangiitis obliterans). Another case presented with a fever of unknown origin in a patient with viral hepatitis C treated with interferon and ribavirin. In patient 5, the initial thrombosis study showed a partial deficiency of protein C that was not confirmed in subsequent tests. Case 7 was initially associated with lupus anticoagulant, although the patient did not report a history of spontaneous abortions or other thrombotic phenomena. A repeat laboratory workup at 6 weeks showed no abnormalities and, therefore, the patient was referred to the hematology department where repeated studies ruled out this initial association.

Patient 3 developed a depressive syndrome, leading to suspicion of a possible associated pancreatic tumor. Computed tomography scans of the chest and abdomen were therefore performed, showing thickening of the gastric wall; however, malignancy was ruled out by gastroscopy.

Deep vein thrombosis was not observed in any patient. Two patients showed signs of chronic venous insufficiency in the legs. No patient was found to have inflammatory bowel disease or Behçet disease.

All patients (except patient 4) had recurrences. The therapeutic options employed included conservative measures such as rest and elastic compression stockings, as well as systemic treatment with nonsteroidal anti-inflammatory drugs, pentoxifylline, corticosteroids, and anticoagulants in the 2 cases associated with Buerger disease.

The mean follow-up time of patients was 3 years (range, 6 months to 5 years).

## Discussion

SMT presents as painful erythematous nodules, usually located on the legs. It can also affect the epigastric, thoracoepigastric, or lateral thoracic veins, resulting in visible or indurated cords in the chest wall, a condition known as Mondor disease.<sup>1</sup> This has also been occasionally reported in the axilla, inguinal region, and penis.<sup>2</sup> After several days, cord-like induration can be palpated. Clinically, the lesions can be confused with conditions such as nodular vasculitis, erythema nodosum, polyarteritis nodosa, cellulitis, or

lymphangitis.<sup>3,4</sup> In our series, lower limb involvement in the form of subcutaneous nodules similar to erythema nodosum was the most common clinical presentation. Patient 7 had a linear erythematous lesion on the chest wall that resembled lymphangitis. SMT was initially diagnosed only in patient 2, who presented infraumbilical subcutaneous nodules.

SMT usually affects the veins located in the superficial subcutaneous tissue. Recent lesions are characterized by predominantly polymorphonuclear inflammatory infiltrates in the vein wall. The polymorphonuclear cells are progressively replaced by lymphocytes and histiocytes, as well as by giant cells on occasion. The thrombus initially occluding the vascular lumen is later replaced by recanalization and fibrosis. The differential histologic diagnosis is performed with polyarteritis nodosa; in this condition, the vessels are arteries that can be recognized by the diameter of the lumen, the thickness of the wall, and the presence of an internal elastic lamina.

The possible association of SMT with various systemic diseases, including occult tumors, makes its diagnosis important. Trousseau was the first to describe the potential association between venous thrombosis and cancer. Various vascular phenomena have preceded the diagnosis of cancer, such as arterial thrombosis, arterial embolism, nonbacterial thrombotic endocarditis, and SMT.<sup>5</sup> The Trousseau sign appears particularly in mucinous adenocarcinomas and is apparently triggered once the circulating mucin secreted by carcinoma cells interacts with platelet and leukocyte selectin (P-selectin and L-selectin). These data may explain why heparin, which is able to inhibit mucin interaction with L-selectin and P-selectin, can improve Trousseau syndrome whereas oral anticoagulants that are vitamin K antagonists are often ineffective.<sup>6</sup>

However, SMT can be diagnosed months or even years before the occult tumor is diagnosed.

Other diseases that have been related to SMT include Buerger disease,<sup>7</sup> Behçet syndrome, inflammatory bowel disease,<sup>8</sup> deep vein thrombosis,<sup>9</sup> coagulation defects potentially leading to a hypercoagulable state, such as protein C or S deficiencies, lupus anticoagulant,<sup>10</sup> or factor XII (Hageman factor) deficiency.<sup>11</sup>

The onset of Mondor disease has been related to direct injuries, strenuous exercise, breast infections,<sup>12</sup> or surgical procedures on the breast.<sup>13</sup> The condition is related to breast cancer in up to 12% of patients.<sup>14</sup>

SMT treatment may yield disappointing results, with frequent recurrences. Measures such as rest and elastic compression stockings may improve the symptoms. In the case of Mondor disease, the lesions tend to resolve within a few days, with a low frequency of recurrence. Most clinicians use anticoagulants only for patients with deep vein disease. In cases of associated tumors, adjuvant anticoagulants (particularly heparin) are used in addition to treatment of the tumor.<sup>6</sup>

## Conclusion

The possible association of SMT with various systemic diseases, including occult tumors, makes its diagnosis important. Our case series shows, however, that the condition is not always easily recognized because it can be confused with other, more common, entities such as cellulitis or erythema nodosum. In fact, the mean time to definitive diagnosis was 10 months. SMT was diagnosed clinically in only 1 patient. Therefore, SMT should be included in the differential diagnosis whenever the patient has recurrent cutaneous nodules with a linear distribution. In our case series, we were unable to find an associated disease in most cases. However, because cancer can present months or years after SMT is diagnosed, follow-up is necessary in these patients.

## Conflicts of Interest

The authors declare no conflicts of interest.

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