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Manuscript

Cutaneous collagenous vasculopathy (CCV) is a rare idiopathic microangiopathy first described in 2000 by Salama and Rosenthal[1], with less than one hundred cases published in the English literature. It is one of the main causes of primary generalized telangiectasias, the other one being Generalized Essential Telangiectasia (GET). Both disorders affect predominantly middle aged women, and share a similar clinical presentation, with cutaneous telangiectasias that first appear on the lower extremities and spread proximally to the trunk and/or upper extremities. Whereas GET can affect the face and mucosae, this is unusual in CCV, but otherwise differential diagnosis warrants a biopsy, showing thickening of the superficial dermal vessel walls in CCV but not in GET.

We present a series of nineteen patients diagnosed with CCV in five different hospitals in northern Spain, and compare their clinical and anatomopathological findings (Table 1) to those previously reported in the English literature (Table 2), in the hopes of drawing attention to the main characteristics of this lesser known entity.

Our population consists of nineteen caucasian individuals, with a mean age of sixty six years old, and equal distribution between genders (ten female, nine male). Almost half of our population (47 %) had three or more comorbidities, the most frequent ones being high blood pressure (HBP), diabetes mellitus type II (DM II) and dyslipidemia. In all cases cutaneous findings consisted of telangiectatic, blanchable, red macules with a reticulated or arborizing linear pattern on dermoscopy (Figure 1A and 1B). In two thirds of patients lesions first appeared in the lower extremities, and spread progressively to involve the upper extremities in approximately half. The other third presented first with lesions distributed along the upper body that later spread to the extremities. Nail beds and mucosal surfaces were spared. Most cases were asymptomatic, only 4 reported mild pruritus. Personal and family history were negative for photosensitivity or bleeding disorders.

Diagnosis was confirmed through a skin biopsy, where dermal blood vessels were moderately dilated and vessel walls thickened by an amorphous, hyaline material, which was highlighted with periodic acid-Schiff (PAS) stain (Figure 2A). Immunostaining for collagen IV was strongly positive (Figure 2B). There was no significant inflammation and no evidence of recent or remote hemorrhage.

We reviewed a total of sixty six cases of CCV published in English literature. Age and gender distribution are similar to our series, with a mean age of fifty nine and a slight female predominance (65 %). There are three published cases of CCV of pediatric onset with ages ranging from thirteen to seventeen (Motegi et al. 2016, Lloyd et al. 2011, Firsowicz et al. 2023). As in our series, HBP, DM II and dyslipidemia were the most common comorbidities, affecting about two thirds of patients. Clinical presentation is most frequently asymptomatic, fine telangiectasias starting on the lower limbs with slow progression to the upper extremities and the trunk. Unusual presentations include annular disposition of telangiectasias (García-Martínez P et al. 2017) and telangiectatic macules and

papules (Conde-Ferreirós et al. 2019). In several cases a progressive darkening of the lesions is described, with a change from bright red to purple more tortuous telangiectasias. Histological findings are similar to those in our series, only exceptionally fibrin thrombi have been reported (Salama et al 2015).

The pathogenesis of CCV is not fully understood. Given the high prevalence among the CCV patients of chronic, acquired, cardiovascular conditions as well as polymedication, the prevalent theory is that these generate a repeated, chronic injury of the microvasculature, causing endothelial hyperplasia and fibrosis. Other individual factors may play a role since the proportion of cardiovascular comorbidities among CCV patients is similar to that of the general population in the same age group. Some authors have suggested a genetic predisposition due to pathogenic variants of genes controlling production and breakdown of collagen [2].

In brief, nineteen new cases of CCV are added to the current literature. In our series, epidemiological, clinical and histopathological findings do not differ substantially from those reported in the literature, indicating the limited spectrum of this condition. CCV is an underdiagnosed disorder due to its lack of symptoms, and its many similarities with GET, but it is likely to be much more common, and should always be considered in the differential diagnosis of generalized telangiectasias. A skin biopsy of the lesions for histopathological examination would allow for a more accurate distinction between GET and CCV, and potentially a better understanding of the pathogenesis of CCV.

Table 1. Clinical characteristics of the 19 patients in this series with Cutaneous Collagenous Vasculopathy

	Sex	Age	Associated medical conditions	Distribution	Symptoms

1	M	43	-	LE, UE	No
2	F	60	Glaucoma, hypothyroidism	LE	No
3	F	61	-	LE	Mild pruritus
4	F	89	HBP, osteoporosis	LE, UE	No
5	F	49	-	LE	No
6	F	53	HBP	Back	No
7	F	91	Pancreatitis, osteoarthritis	LE	Mild pruritus
8	M	66	Parkinson's disease, stroke, HBP, DLP	UE, LE	No
9	M	68	DLP, HBP, hyperuricemia, prostate cancer	LE	No
10	F	89	Pancreatitis, colelitiasis	LE	No
11	M	77	HBP, DLP, CVA	LE, ABD, UE	No
12	F	70	HBP, DLP, DM-II	UE	No
13	M	43	HBP, DLP, AF, HHD, facial paralysis	ABD	No
14	M	68	HBP, hyperuricemia	UE	No
15	F	54	Hypothyroidism, arthrosis	Breasts	No
16	F	63	-	LE	Mild pruritus
17	M	78	Essential thrombocytosis	LE, ABD, UE	No
18	M	74	Prostate adenoma, Necrotizing granulomatous lymphadenitis, MGUS	LE, ABD, UE	Mild pruritus
19	M	66	HBP, DLP, SVT, diverticular disease, hepatic steatosis, Gilbert’s syndrome,	ABD	No

M (Male); F (Female); LE (lower extremities); UE (upper extremities); HBP (high blood pressure); DLP (dyslipidemia); CVA (cerebrovascular accident); ABD (abdomen); DM-II (Type 2 diabetes mellitus); AF (atrial fibrillation); HHD (hipertensive heart disease); MGUS (Monoclonal gammopathy of undetermined significance); SVT (supraventricular tachycardia).

Table 2. Comparison of the clinical characteristics between the 66 cases of Cutaneous Collagenous Vasculopathy reported in the literature and the 19 patients in this series.

		Literature (66)	**Case series (19)**
Age	Average (years)	59	66
	Range (years)	13-92	43-91
Sex	Female	44 (65.1 %)	10 (52 %)
	Male	23 (34.8 %)	9 (47 %)
Race	Caucasian	36 (54%)	19 (100 %)
	Asian	2 (3 %)	-
Associated medical conditions	3 or more conditions	29 (43 %)	9 (47 %)
	Cardiovascular (HBP, DLP, DM-II)	32 (48 %)	9 (47 %)
Medication	3 or more medications	20 (30 %)	8 (42 %)
	ACEi/AIIRA	13 (19 %)	6 (31 %)
	Statins	13 (19 %)	3 (15 %)
Symptoms	Asymptomatic	59 (89 %)	15 (79 %)
	Mild pruritus	6 (10 %)	4 (21 %)
	Hypothermia	1	-
Time to diagnosis	Average (years)	8	4

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