ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Is there a correlation between the CEAP score and the histopathological findings in varicose disease?

A. MIRONIUC[1)], LAURA PALCĂU[1)], LILIANA ROGOJAN[2)], SANDA MICULA[3)], CLAUDIA GHERMAN[1)]

[1)]*Surgical Clinic II, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*
[2)]*Department of Pathomorphology, Emergency County Hospital, Cluj-Napoca*
[3)]*Department of Numerical and Statistical Calculus, Faculty of Mathematics and Computer Science, "Babeş-Bolyai" University, Cluj-Napoca*

Abstract

Background: Varicose disease continues to represent an interesting subject. The factors triggering and maintaining vascular and cutaneous tissues alterations in chronic venous insufficiency are not fully known. *Patients and Methods*: This is a prospective, statistical analysis study, performed in a consecutive series of 40 patients with varicose disease admitted and treated at the Surgical Clinic II, Cluj-Napoca. The aim of the paper is to evidence histopathological (HP) changes in the vein wall, as well as to correlate histopathological findings, classified into stages, with the clinical stage of chronic venous insufficiency (CEAP classification). Statistical analysis was performed using the Fischer *F*-test for the comparison of the variances of two selections and the Student *t*-test for the comparison of the means. For correlation, Pearson's simple correlation coefficient was used. The software used was Excel and Matlab 7. *Results*: Following the statistical analysis, the mean of CEAP values was found to be higher than the mean of the histopathological stage values in all patients included in the study and in the different risk groups. The values of Pearson's linear correlation coefficient between CEAP values and histopathological stage values did not generally show a statistically significant correlation. *Conclusions*: CEAP classification remains the main pillar in the diagnosis and the treatment of varicose disease, even if there are some dissimilarities between the clinical appearance and the histopathological results. The presence of a correlation between histological and clinical aspects in varicose disease remains uncertain.

Keywords: varicose disease, CEAP classification, histological findings.

Introduction

Osteoporosis varicosity is a complex venous pathology affecting the lower extremities. The exact etiology and physiopathology of varicose vein disease remain, however, unclear [1]. Although four theories have been put forward as potentially causative mechanisms, none yet has been established. However, there is strong evidence accumulated over the last ten years supporting the "weakening of the vein wall" theory as the initial pathogenetic mechanism [2]. The status of the long saphenous vein (LSV) recently has been investigated, because this vein is the most favorable conduit for bypass in cardiac and vascular surgery. These studies [3–8] have shown that even clinically undiseased LSVs suitable for grafting have histological changes in their walls, indicating unsuspected disease. However, all these studies are based on histological investigation of the LSV wall changes, and none of them studied these changes in relation to the CEAP classification (Clinical signs ('C'), the various Etiologies ('E'), Anatomical sites ('A') and Pathophysiological disorders ('P'), and especially to the clinical status of this classification, which is based on objective clinical signs of chronic venous disease according to seven classes (Table 1).

Table 1 – ***Clinical classes of the CEAP classification***

Class	Description
C0	No visible or palpable sign of venous disease.
C1	Telangiectases or reticular veins.
C2	Varicose veins.
C3	Edema.
C4	Skin changes ascribed to venous disease (pigmentation, venous eczema, lipodermatosclerosis).
C5	Skin changes as defined above with healed ulcer.
C6	Skin changes as defined above with active ulcer.

We started this study from the premise that morphopathological alterations precede the clinical ones, thus advanced parietal remodeling would be more frequently found in early clinical stages. In order to demonstrate this hypothesis, the comparison between the morphopathological status and the clinical CEAP score is of paramount importance, especially in the view of the impact on therapy.

Aim of the study

If several studies [9, 10] were based on the assumption that a clinically non-varicose vein was normal, our

study aimed at evidencing the morphopathological alterations independently from the clinical status (presence or absence of varicose beds). If the results of our study will reveal no correlation between parietal alterations and the clinical manifestations of the varicose disease, they will influence therapeutic management and will bring to the forefront the decision regarding initiation of therapy. We refer to the preventive treatment depending on the individual susceptibility to develop the disease (taking into account family history and risk factors).

Patients and Methods

This is a prospective, statistical analysis study, performed in a consecutive series of 40 patients with varicose disease admitted to and treated at Surgical Clinic II, Cluj-Napoca. The only mandatory and defining criterion of the patient selection was the presence of varicose disease, in the context of chronic venous insufficiency, regardless of the CEAL score. Patients were selected independently from the presence or absence of risk factors for varicose disease, with the purpose of checking whether histopathological changes were more advanced in the patients presenting such risk factors. The aim of the paper is to evidence histopathological (HP) changes in the vein wall (by in-operative sampling of vein wall fragments from the arch of the internal saphenous vein (ISV), communicating veins, perforating veins, in Hematoxylin–Eosin (HE) staining, as well as to correlate histopathological results, classified into stages, with the clinical stage of chronic venous insufficiency (CEAP classification).

Statistical analysis was performed in the group included in the study. The objective was to evidence a statistical correlation between the values of the clinical stage and those of the histological stage in all patients and in the different groups of risk factors. Patients with a positive family history were compared to those without a history of varicose veins and patients with arterial hypertension were compared to those without hypertension. Obese patients were compared to normal weight patients and patients with *post partum* varicose veins were compared to those with varicose veins unrelated to pregnancy. Patients with bilateral varicose veins were compared to those with varicose veins in one pelvic limb and patients with preoperative venotrophic treatment were compared to patients without treatment.

Statistical analysis was performed using the Fischer F-test for the comparison of variances of two selections and the Student t-test for the comparison of the means. The p-values of the tests are one-tailed. For p-values >0.05, differences are not significant (NS), for $0.01< p<0.05$, differences are significant, for $0.001<p<0.01$, differences are distinctly significant, and for $p<0.001$, differences are highly significant. For correlation, Pearson's simple correlation coefficient was used. The software programs used were Excel and Matlab 7.

Results

The results of the current study are provided for a number of 40 patients. The characteristics of patients are enumerated in the first column of the Table 2.

The correlation of the clinical stage with the histopathological stage is schematized in Table 3.

The stages of parietal remodeling are: hypertrophy of the muscle fibers with the excessive development of connective tissue (I) (Figure 1); intimal hyperplasia (II) (Figure 2), mass sclerosis (III) (Figure 3), the hyalinization of the fundamental substance or calcareous degeneration (IV) (Figure 4) and finally, indurated cellulitis (V).

Table 2 – ***Results of statistical analysis***

No. of cases (%)	CEAP values (M ± SD)	Histopathological values (M ± SD)	Comparison of CEAP and histopathological *p*-values	Comparison of CEAP and histopathological correlation coefficient
Total, n=40	3.78 ± 0.92	2.9 ± 1.15	$p<0.001$	$r=-0.09$
High blood pressure 10 (25%)	4 ± 0.82	2.7 ± 1.25	$p<0.01$	$r=-0.11$
Normal blood pressure 30 (75%)	3.7 ± 0.95	2.97 ± 1.13	$p<0.01$	$r=0.21$
Previous venotrophic treatment 15 (37.5%)	3.87 ± 0.99	2.67 ± 1.11	$p<0.01$	$r=0.08$
No previous venotrophic treatment 25 (62.5%)	3.72 ± 0.89	3.04 ± 1.17	$p<0.05$	$r=-0.19$
Positive family history of varicose disease 24 (60%)	3.67 ± 0.92	2.75 ± 1.19	$p<0.01$	$r=0.04$
No family history of varicose disease 16 (40%)	3.94 ± 0.93	3.12 ± 1.09	$p<0.05$	$r=-0.39$
Post partum 19 (47.5%)	3.63 ± 0.96	2.84 ± 1.3	$p<0.05$	$r=-0.27$
Not pregnancy-related 21 (53.5%)	3.9 ± 0.89	2.95 ± 1.02	$p<0.01$	$r=0.1$
Overweight 18 (45%)	4 ± 0.9	2.72 ± 1.23	$p<0.001$	$r=-0.26$
Not overweight 22 (55%)	3.59 ± 0.9	3.05 ± 1.09	$p<0.05$	$r=0.12$
Bilateral varices 11 (27.5%)	4.18 ± 1.25	3.18 ± 1.17	$p<0.05$	$r=-0.44$
Unilateral varices 29 (72.5%)	3.62 ± 0.73	2.79 ± 1.15	$p<0.001$	$r=0.03$

Table 3 – *Clinical–histopathological correlations*

CEAP stage	HP stage (no. of cases)
C3	HP I (2)
	HP II (6)
	HP III (3)
	HP IV (7)
C4	HP I (1)
	HP II (4)
	HP III (4)
	HP IV (7)
	HP V (1)
C5	HP III (1)
C6	HP I (1)
	HP II (2)
	HP IV (1)

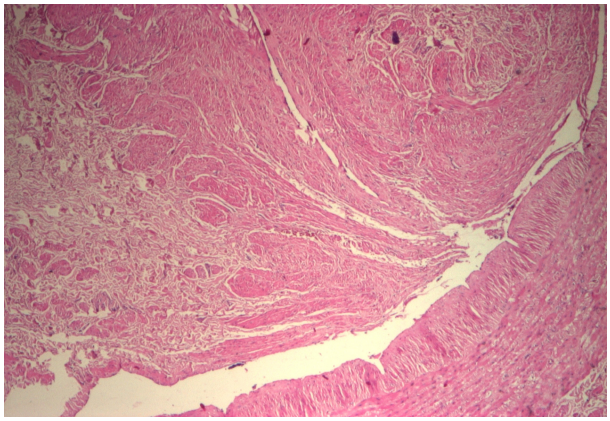

Figure 1 – *Intimal hypertrophy (HE stain, ×20).*

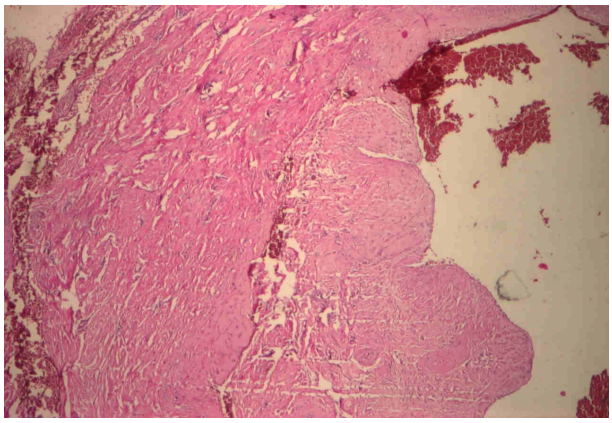

Figure 2 – *Intimal hyperplasia (HE stain, ×20).*

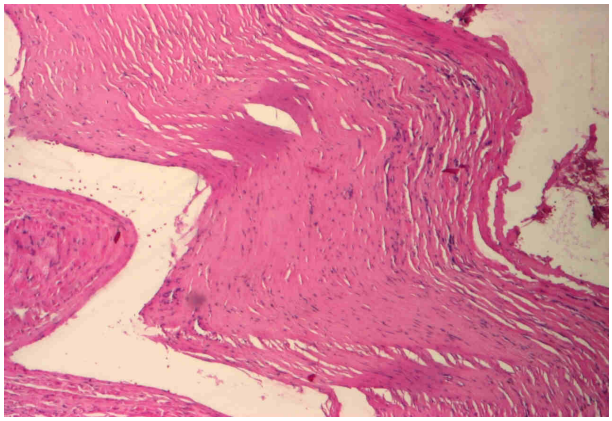

Figure 3 – *Transmural fibrosis (HE stain, ×40).*

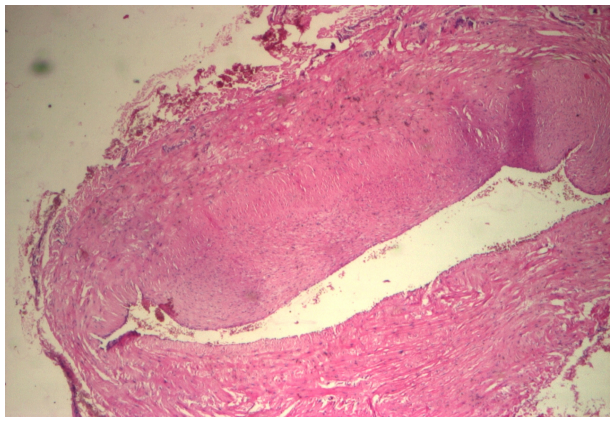

Figure 4 – *Mass sclerosis and calcareous degeneration (HE stain, ×20).*

Table 2 also shows the values of the CEAP stage and the histopathological stage in all patients and by groups of risk factors (columns II and III). The values are given as mean ± standard deviation. Then the values of the CEAP and HP stages were compared per total as well as for each category of risk factor. Student *t*-tests were performed to compare the means of CEAP and HP values. In each row (for the corresponding category), column four contains the *p*-values of those tests. Significant differences are seen in each category. These differences are significant in the case of patients without a history of venotrophic treatment, without a positive family history, *post partum*, with normal weight and bilateral varicose veins ($p<0.05$). Differences are distinctly significant in the case of patients with arterial hypertension, without arterial hypertension, with a history of venotrophic treatment, with a positive family history unrelated to pregnancy ($p<0.01$). Also, differences are highly significant in all patients as well as in the case of overweight patients and patients with unilateral varicose veins ($p<0.001$). The last column contains the values of Pearson's linear correlation coefficient between CEAP values and histopathological stage values. In general, no statistically significant correlation is seen. The strongest correlation is found between the CEAP and the histopathological stage values in patients with bilateral varicose veins ($r=0.44$) and patients without a positive family history ($r=-0.39$), while the weakest correlation appears in the case of patients with unilateral varicose veins ($r=0.03$) and those with a positive family history ($r=0.04$).

Figure 5 shows the scatterplot of the data, per total. Each point corresponds to a patient (of the 40 that were studied), the X-coordinate being the HP value and the y-coordinate the CEAP value. As expected from the small value of the correlation coefficient ($r=-0.09$; Table 2, first row, first column), the plot does not exhibit a linear trend, so there does not seem to be any linear correlation between the CEAP and HP values. The line of regression is also displayed in Figure 5.

Because of the repetitive nature of the data, many points in the scatterplot coincide, which is why we showed the individual values of the CEAP and HP stages in Figure 6. It also clearly shows that the CEAP stage values are significantly higher than the ones corresponding to the HP stage.

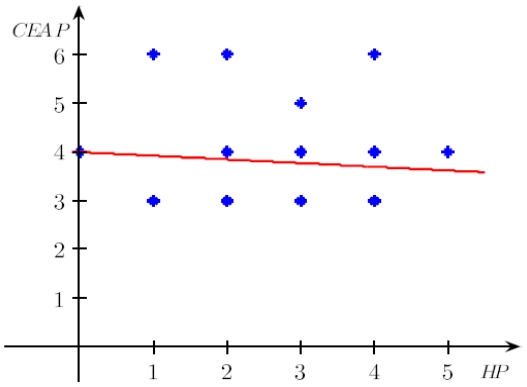

Figure 5 – ***The scatterplot of the data.***

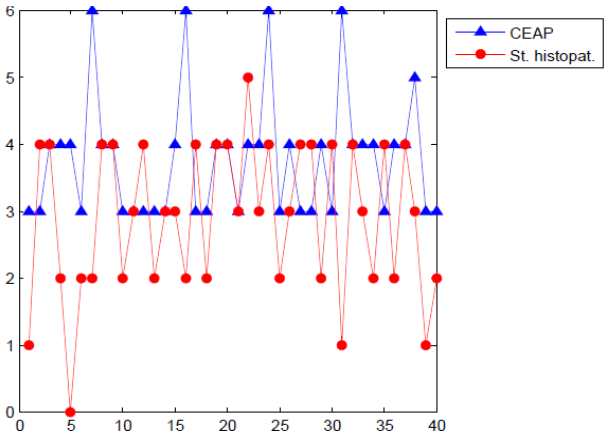

Figure 6 – ***The scatterplot of the data.***

There were no statistically significant differences on the separate analysis of the values of clinical and histopathological classification in the above-mentioned groups.

Discussion

Varicose disease currently remains a subject of great interest. The factors of the initiation and progression of vascular and cutaneous tissue alterations in chronic venous insufficiency are not completely understood.

The CEAP classification remains the main pillar in the diagnosis and treatment of varicose disease, in spite of the presence of some dissimilarity between clinical appearance and histopathological findings. The presence of a correlation between histological and clinical aspects in varicose disease remains uncertain [11, 12]. The histopathological changes in the various components of the vein wall seem to be correlated with functional and morphological changes [1].

An interesting aspect to monitor is the presence of fibrosis, which seems to be independent of the presence or absence of venous reflux or chronic venous insufficiency, regardless of the saphenous segment [2]. Cell changes are more numerous at the level of proximal varicose segments. The fundamental characteristic of parietal changes is represented by the high degree of medial and intimal hypertrophy [1, 13].

The study could not detect the presence of a correlation between the clinical CEAP stage and the histopathological stage in varicose disease. Statistical significance is referring to the fact that the mean of CEAP values was higher than the mean of the histopathological stage values. Significant differences were found in the case of patients without a history of venotrophic treatment, without a positive family history, *post partum*, with normal weight and with bilateral varicose veins ($p<0.05$). Distinctly significant differences were found in the case of patients with arterial hypertension, without arterial hypertension, with a history of venotrophic treatment, with a positive family history unrelated to pregnancy ($p<0.01$). Highly significant differences were found in all patients, as well as in the case of overweight patients and patients with unilateral varicose veins ($p<0.001$).

The strongest correlation was found between the CEAP and the histopathological stage values in patients with bilateral varicose veins ($r=0.44$) and patients without a positive family history of varicose disease ($r=-0.39$), while the weakest correlation appeared in the case of patients with unilateral varicose disease ($r=0.03$) and patients without a positive family history ($r=0.04$). It should be mentioned that patients assigned to CEAP stages 5 and 6 had histopathological changes classified as HP stages II and III. One case assigned to CEAP class 6 had mass fibrosis and calcareous degeneration.

The results presented in this study emphasize the multi-factorial character of varicose disease, thus completing the pathophysiological picture. Once the primary role of morphopathological changes has been demonstrated in relation to the clinical manifestations, the therapeutic implications become obvious. No definite correlation between the morphopathological changes and clinical stages (parietal alterations preceding clinical status) has been established until the present, and further research is necessary. Moreover, if histopathological changes are more advanced in the patients presenting risk factors (predisposing or triggering), preventive therapy might be an issue to take into account.

It is also interesting to follow up venous wall remodeling in the patients with venotrophic treatment before surgery; our study has no clear conclusion in this respect. However, it seems that these patients present an early stage of venous wall alterations; therefore, further investigation could provide information on the benefits of venotrophic therapy in varicose disease.

Conclusions

The results of this study are interesting and may be subject of debate; however, more extensive trial studies are necessary in order to obtain statistically specific and sensitive results that lend themselves to generalizations.

We may conclude that now histopathological changes cannot be correlated with clinical appearance, which is why further studies are required.

References

[1] Somers P, Knaapen M, *The histopathology of varicose vein disease*, Angiology, 2006, 57(5):546–555.

[2] Labropoulos N, Giannoukas AD, Stavridis G, Bailey D, Glenville B, Nicolaides AN, *Insights in the development of primary venous reflux*, Vasc Endovasc Surg, 1999, 33(2):191–196.

[3] Thiene G, Miazzi P, Valsecchi M, Valente M, Bortolotti U, Casarotto D, Gallucci V, *Histological survey of the saphenous vein before its use as autologous aortocoronary bypass graft*, Thorax, 1980, 35(7):519–522.

[4] Milroy CM, Scott DJA, Beard JD, Horrocks M, Bradfield JW, *Histological appearances of the long saphenous vein*, J Pathol, 1989, 159(4):311–316.
[5] Panetta TF, Marin ML, Veith FJ, Goldsmith J, Gordon RE, Jones AM, Schwartz ML, Gupta SK, Wengerter KR, *Unsuspected preexisting saphenous vein disease: an unrecognized cause of vein bypass failure*, J Vasc Surg, 1992, 15(1):102–112; discussion 110–112.
[6] Marin ML, Gordon RE, Veith FJ, Panetta T, Wengerter K, Gupta S, *Ultrastructure of human saphenous vein (SV) – features which may contribute to intimal hyperplasia and vein graft failure*, FASEB J, 1991, 5(4):A529.
[7] Davies AH, Magee TR, Baird RN, Sheffield E, Horrocks M, *Pre-bypass morphological changes in vein grafts*, Eur J Vasc Surg, 1993, 7(6):642–647.
[8] Giannoukas AD, Stavridis GT, Labropoulos N, Bailey D, Glenville B, Nicolaides AN, *Quality of the long saphenous vein conduits used for coronary artery bypass grafting operations*, Vasc Endovasc Surg, 1997, 31(6):757–760.
[9] Porto LC, da Silveira PRM, de Carvalho JJ, Panico MD, *Connective tissue accumulation in the muscle layer in normal and varicose saphenous veins*, Angiology, 1995, 46(3):243–249.
[10] Bouissou H, Julian M, Pieraggi MT, Maurel E, Thiers JC, Louge L, Structure of healthy and varicose veins. In: Vanhoutte PM (ed), *Return circulation and norepinephrine: an update*, John Libbey Eurotext, Paris, 1991, 139–150.
[11] Aravind B, Davies AH, *Role of inflammation in varicose vein aetiology*, Phlebology, 2004, 19(2):55–56.
[12] Buján J, Jiménez-Cossio JA, Jurado F, Gimeno MJ, Pascual G, García-Honduvilla N, Dominguez B, Bellón JM, *Evaluation of the smooth muscle cell component and apoptosis in the varicose vein wall*, Histol Histopathol, 2000, 15(3):745–752.
[13] Corcos L, De Anna D, Dini M, Macchi C, Ferrari PA, Dini S, *Histopathology of great saphenous vein valves in primary venous insufficiency*, Phlebolymphology, 2004, 47:304–311.
[14] Mironiuc A, Palcău L, Andercou O, Rogojan L, Todoran M, Gordan G, *Corelații clinico-histopatologice ale modificărilor parietale venoase în insuficiența venoasă cronică*, Chirurgia, 2008, 103(3):313–316.

Corresponding author
Aurel Mironiuc, Professor, MD, PhD, Surgical Clinic II, "Iuliu Haţieganu" University of Medicine and Pharmacy, 4–6 Clinicilor Street, 400023 Cluj-Napoca, Romania; Phone +40743–082 993, e-mail: aurelmironiuc@yahoo.com

Received: June 16th, 2010

Accepted: January 10th, 2011