Sex-related differences in carotid plaque features and inflammation

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Objective: **Severe carotid stenosis is a frequent cause of stroke in both men and women. Whereas several sex-related comparisons are available on coronary atherosclerosis, there are few data appraising gender-specific features of carotid plaques. We aimed to systematically compare the pathology and inflammatory features of carotid plaques in men vs women.**

Methods: **Carotid plaque specimens were collected from patients undergoing surgical endarterectomy for asymptomatic or symptomatic carotid stenosis. Histologic analysis was performed, as well as measurements of plaque composition and inflammation.**

Results: **A total of 457 patients were included (132 women, 325 men). Baseline analyses showed a greater prevalence of hypercholesterolemia, hypertension, and former smoking status in women, despite a higher Framingham Heart Score in men (all $P < .05$). Women had a lower prevalence of thrombotic plaques, smaller percentage area of necrotic core, and hemorrhage extension (all $P < .05$). Plaque inflammation analysis showed a lower concentration of inflammatory and, in particular, of macrophage foam cells in the plaque cap of women (both $P < .05$). These differences were, however, no longer significant at multivariable analysis, including several baseline features, such as symptom status and stenosis severity.**

Conclusions: **Carotid plaques seem significantly different in women and men, but the main drivers of such pathologic differences are baseline features, including stenosis severity and symptom status. (J Vasc Surg 2013;57:338-44.)**

It is well recognized that cardiovascular diseases (CVDs) represent an important burden in Western society. An estimated 82 million Americans have at least one type of CVD, and of these, about 7 million have had a stroke. Statistics have shown that the vast majority of stroke is caused by ischemia (87% compared to 13% of intracerebral or subarachnoid hemorrhages).[1]

It is now widely accepted that carotid atherosclerosis and subsequent stenosis is a relevant cause of ischemic stroke.[2] Carotid atheroma was described as a possible cause of stroke already at the beginning of the century, and this was finally proven by large multicenter trials demonstrating stroke reduction after carotid endarterectomy (CEA) of severe stenosis.[3-7] However, men and women are not affected in the same way[1] and gender difference has been reported for stroke as well as for other CVDs.[8-10] Even though many authors have focused their attention on carotid atherosclerosis, just a few works have addressed sex-related differences in this vascular bed. Thus, most of our knowledge on gender difference in atherosclerosis derives from analysis carried out on coronary arteries.[11,12] In particular, it is well recognized that men develop active coronary atherosclerosis and associated acute lesions earlier in life, whereas premenopausal women seem to be more resistant to coronary artery disease (CAD). Moreover, atherosclerosis in men presents distinct inflammatory and histologic features when compared to women.[13-15] Because relevant gender-related differences have been highlighted in coronary arteries, could the same be true in carotid vessels? Thus, we aimed to systematically compare carotid plaque specimens derived from CEA of both men and women to search for sex-related distinctions in plaque morphology.

METHODS

Case selection. Our population comprised a total of 457 specimens from symptomatic (major stroke or transient ischemic attack [TIA]) and asymptomatic patients submitted to surgical CEA at the University of Tor Vergata (Rome, Italy). Informed consent was obtained from the subjects for data collection.

The sampling collection and analysis methods have been previously reported.[16] Data regarding patient presentation, including risk factors and symptoms were recorded. Hypertension, hyperlipidemia, and diabetes were defined by case history, drug treatment, or available analysis.

Previous CAD and obstructive peripheral vascular disease, coronary artery bypass graft, and preoperative use of aspirin and statins were assessed from clinical history. Hy-

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pertension was diagnosed in patients with positive clinical history of systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg, or those receiving antihypertensive treatment at the time of CEA. Diabetes mellitus was diagnosed in patients with fasting blood glucose >126 mg/dL and/or on oral treatment or insulin therapy. Patients with tobacco dependence were categorized as smokers and former smokers. Former smokers who had stopped smoking for <5 years were considered as smokers and patients who had not smoked for >15 years were considered as nonsmokers. Hypercholesterolemia was diagnosed in those with total cholesterol level >200 mg/dL (>5.18 mmol/L), regardless of statin therapy. Patients were defined as with low high-density lipoprotein-cholesterol if this was <40 mg/dL in men or <50 mg/dL in women. Hypertriglyceridemia was diagnosed in patients with serum triglycerides levels >150 mg/dL (>1.70 mmol/L). Abdominal obesity was diagnosed in patients with a waist circumference >102 cm in men or >88 cm in women. In addition, the Framingham Risk Score was calculated using an algorithm that included age, gender, smoking status, and presence of diabetes as dichotomous parameters, as well as total cholesterol, high-density lipoprotein-cholesterol, and diastolic and systolic blood pressure using the categories defined in the Framingham equation.

Major stroke was defined as a clinical syndrome characterized by rapidly developing focal or global symptoms in the distribution of symptomatic carotid artery, without significant clinical improvement within 7 days; stroke had to be of vascular origin, and other causes as hemorrhage were excluded by brain computed tomography study. TIA was defined as recent (<120 days before surgery) occurrence of any sudden focal neurological deficit that disappeared completely within 24 hours, without previous stroke. Asymptomatic patients never reported neurological symptoms or cerebral lesions at computed tomography. All asymptomatic patients showed a carotid stenosis >60%. Stenosis severity was appraised with both North American Symptomatic Carotid Endarterectomy Trial criteria and at pathology.

Histology. Intraoperatively, carotid plaques were removed en bloc by conventional arteriotomy to preserve entire plaque structure, as previously reported.[16] When a carotid sample was fragmented, the case was excluded from the study. Thus, only intact cases were analyzed. Then, samples were fixed immediately upon removal in 10% buffered formalin for 24 hours. After decalcification, if necessary, specimens were cut transversely every 5 mm, embedded in paraffin, and stained with hematoxylin-eosin and Movat pentachrome stains. Each segment was removed and numbered sequentially to reconstruct the entire plaque length by sequential slices. For each plaque, three to 10 sections were examined according to the extension of the plaque (mean 5 sections per artery). In this way, the entire plaque was evaluated for the presence of an acute or organized thrombosis, plaque rupture or erosion, extension of necrotic core, calcification, and intraplaque hemorrhage.

Table I. Baseline features

	Women (n = 132)	*Men (n = 325)*	P *value*
Age (years)	69.9 ± 7.2	69.6 ± 7.0	.768
Smoking history			.002
Current	32 (24.2%)	96 (29.5%)	
Former	71 (53.8%)	117 (36.0%)	
Ever	29 (22.0%)	112 (34.5%)	
Hypercholesterolemia	89 (67.4%)	183 (56.3%)	.028
Hypertension	61 (67.0%)	121 (53.1%)	.023
Serum fibrinogen (mg/dL)	365.1 ± 140.6	335.3 ± 93.0	.420
Total number of risk factors	2.9 ± 1.4	2.7 ± 1.5	.228
FHS	17.3 ± 7.4	27.3 ± 11.3	<.001
Statin therapy	42 (35.6%)	87 (29.6%)	.277
Symptomatic status			.178
Asymptomatic	71 (53.8%)	149 (45.8%)	
TIA	27 (20.5%)	92 (28.3%)	
Stroke	34 (25.8%)	84 (25.8%)	
Stenosis severity at preoperative assessment	84.7% ± 9.2%	84.3% ± 9.8%	.741

FHS, Framingham Heart Score; *TIA,* transient ischemic attack.

Two pathologists evaluated all histologic components (intraobserver and interobserver reliability >98%). The presence of acute or organized thrombosis, plaque rupture or erosion, extension of necrotic core, calcification, and intraplaque hemorrhage was evaluated for each plaque. The immunohistochemical study characterized inflammatory cells present in the cap of ruptured plaques, using the CD68 and CD3 monoclonal antibodies. Cell counting was performed at a magnification of >400 using a test grid with an area of 0.22 mm^2. An average of 10 fields per section was counted.

Plaque classification. Plaques were classified according to the modified American Heart Association atherosclerosis classification[12,16] into three categories: thrombotic, vulnerable, and stable plaques. Thrombotic plaques included the following plaque types: (a) plaque rupture with luminal thrombus, (b) ulceration, (c) erosion, (d) calcified nodule, and (e) organizing thrombus. Vulnerable plaque or thin-cap fibro-atheroma (TCFA) was characterized by a fibrous cap <165 μm thick heavily infiltrated by macrophages, CD68 positive (>25 per high magnification field), without plaque rupture.[17] Specifically, as reported previously,[16] a thrombotic plaque was defined by the presence of an acute thrombus constituted of platelets or fibrin on the plaque surface, and characterized by lamination with or without red and white interspersed cells. Thrombosis was divided into two categories: (1) thrombosis associated with plaque rupture and (2) erosion. Plaque rupture was defined as a complete disruption of the fibrous cap over a lipid core with contact of an acute thrombus with the lipid pool. Superficial erosion was defined as plaque disendothelization, associated with the presence of an acute thrombus in direct contact with the subepithelial tissue of the cap without any contact with the lipid pool demonstrated in serial

Table II. Plaque features

	Women (n = 132)	*Men (n = 325)*	P *value*
Plaque location			.687
Common carotid	12 (28.6%)	28 (21.7%)	
Bifurcation	22 (52.4%)	75 (58.1%)	
Internal carotid	8 (19.0%)	24 (18.6%)	
Plaque classification			.034
Rupture with luminal thrombus	11 (8.3%)	25 (7.7%)	
Ulceration	19 (14.4%)	67 (20.6%)	
Erosion	0	1 (0.3%)	
Calcified nodule	7 (5.3%)	7 (2.2%)	
Organized thrombus	7 (5.3%)	37 (11.4%)	
TCFA	22 (16.7%)	50 (15.4%)	
Healed plaque	15 (11.4%)	52 (16.0%)	
Stable fibrocalcific	51 (38.6%)	86 (26.5%)	
Any thrombotic plaques	44 (40.0%)	137 (49.8%)	.013
Minimum cap thickness (μm)	143.2 ± 117.8	131.7 ± 94.1	.612
Percentage area of necrotic lipid core	49.2 ± 18.7	56.2 ± 17.7	.010
Calcium-lumen distance (μm)	866.7 ± 721.5	1458.5 ± 1461.6	.144
Calcified area			.227
>5% of plaque area	41 (64.1%)	85 (51.5%)	
1%-5% of plaque area	11 (17.2%)	40 (24.2%)	
No calcifications	12 (18.8%)	40 (24.2%)	
Hemorrhagic area			.022
>10% of plaque	26 (42.6%)	98 (63.2%)	
1%-10% of plaque	15 (24.6%)	23 (14.8%)	
No hemorrhage	20 (32.8%)	34 (21.9%)	

TCFA, Thin-cap fibroatheroma.

sections. Organized thrombus was characterized by fibrous tissue, sometimes stratified, associated with a typical angiomatosis, with a network of large, thin-walled vascular channels, and a variable number of macrophagic cells loaded with hemosiderin, visible as scattered brown refractive pigments. Stable plaques were divided in fibrocalcific and healed plaques. Fibrocalcific plaques showed a thick fibrous cap (>165 μm) associated to the presence of calcification and a variable necrotic core. Healed plaques were defined as those showing multilayers of fibrous tissue and lipid rich necrotic core.

Statistical analysis. Data were analyzed using SPSS version 11.0 (SPSS, Chicago, Ill) software. The Pearson χ^2 test was used to assess the differences in the frequency of thrombosis, cap rupture and cap erosion, and risk factors between the groups. The *t*-test for unpaired samples was used to evaluate differences in age, grade of angiographic stenosis, and degree of inflammatory infiltrate between the groups. Multivariable linear regression analysis was performed to adjust bivariate estimates, including all covariates associated at bivariate analyses with gender with $P < .10$: smoking status, hypercholesterolemia, hypertension, Framingham Heart Score (FHS), plaque classification, thrombotic plaque, percentage area of necrotic lipid core, and hemorrhage extension, plus stenosis severity and symptom status, given their pivotal importance in carotid atherosclerosis, and R^2 was computed using gender as the only independent variable. Any *P* value < .05 was considered statistically significant.

RESULTS

Risk factors. A total of 457 patients were included, 132 women and 325 men. Baseline features are summarized in Table I. Mean age was 69 years and was not statistically different between groups. Cardiovascular risk factors were recorded and the total number of risk factors per patient showed no statistical difference ($P = .228$). However, specific risk factors differed significantly between genders: men had a higher prevalence of current and previous smoking, whereas women presented with higher incidence of hypercholesterolemia, hypertension, and former smoking history (all $P < .05$). Despite this, men had a higher FHS ($P < .001$). Fibrinogen serum levels did not differ between men and women ($P = .420$). Approximately one third of patients were on statin therapy, with no significant difference ($P = .277$). Plaque thrombosis location was mainly at the bifurcation site in both genders. The maximal luminal stenosis showed no significant difference between men and women ($P = .742$).

Stenosis severity at preoperative assessment was 84.3% ± 9.8% in men and 84.7% ± 9.2% in women ($P = .74$). Further analysis according to symptom status yielded the following results: 84.5% ± 8.4% for asymptomatic disease, 81.7% ± 10.9% for TIA, and 85.5% ± 10.5% for stroke in men, and 82.4% ± 9.5% for asymptomatic disease, 88.5% ± 6.3% for TIA, and 87.4% ± 8.6% for stroke in women (P = not significant).

Table III. Plaque inflammation features at bivariate analysis in the overall cohort and in key subgroups

	Women	*Men*	P *value*
Overall analysis			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	29.3 ± 20.0	36.3 ± 20.4	.017
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	26.0 ± 20.2	34.1 ± 25.8	.028
Foam cells (CD68 positive) in the cap/mm^2	19.3 ± 16.0	27.1 ± 22.7	.009
T-lymphocytes (CD3 positive) in the cap/mm^2	8.5 ± 9.9	7.4 ± 6.1	.541
Asymptomatic patients			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	15.5 ± 10.5	26.6 ± 15.7	.001
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	13.9 ± 10.9	22.2 ± 14.4	.009
Foam cells (CD68 positive) in the cap/mm^2	10.2 ± 7.4	16.6 ± 10.4	.008
T-lymphocytes (CD3 positive) in the cap/mm^2	4.9 ± 5.9	5.4 ± 4.6	.682
Patients with TIA			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	25.6 ± 19.4	35.0 ± 16.0	.117
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	27.0 ± 26.9	29.1 ± 14.6	.836
Foam cells (CD68 positive) in the cap/mm^2	18.9 ± 9.1	22.3 ± 14.3	.694
T-lymphocytes (CD3 positive) in the cap/mm^2	16.7 ± 21.5	6.7 ± 6.5	.134
Patients with stroke			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	46.5 ± 15.2	47.6 ± 21.5	.813
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	42.0 ± 18.2	47.9 ± 31.0	.417
Foam cells (CD68 positive) in the cap/mm^2	30.1 ± 17.7	37.4 ± 27.7	.264
T-lymphocytes (CD3 positive) in the cap/mm^2	12.3 ± 11.4	9.5 ± 6.5	.200
Patients with 50% to 69% stenosis			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	22.6 ± 22.9	35.1 ± 15.8	.205
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	19.6 ± 24.9	34.7 ± 14.4	.115
Foam cells (CD68 positive) in the cap/mm^2	12.7 ± 14.1	27.5 ± 13.6	.073
T-lymphocytes (CD3 positive) in the cap/mm^2	6.9 ± 11.1	8.4 ± 4.0	.664
Patients with 70% to 89% stenosis			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	28.2 ± 14.2	32.6 ± 21.4	.439
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	27.2 ± 16.4	28.6 ± 23.7	.828
Foam cells (CD68 positive) in the cap/mm^2	21.9 ± 12.2	21.9 ± 19.9	.994
T-lymphocytes (CD3 positive) in the cap/mm^2	9.2 ± 5.4	6.8 ± 6.1	.192
Patients with ≥90% stenosis			
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	27.4 ± 19.5	25.8 ± 22.2	.017
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	25.8 ± 22.2	36.1 ± 25.8	.077
Foam cells (CD68 positive) in the cap/mm^2	18.9 ± 19.2	28.8 ± 22.1	.052
T-lymphocytes (CD3 positive) in the cap/mm^2	8.0 ± 11.3	7.7 ± 6.6	.876

TIA, Transient ischemic attack.

Histologic examination. The most relevant features derived from carotid plaque specimens' analysis are reported in Table II.

Types of atherosclerotic plaques had distinct features showing a relevant gender difference ($P = .034$). Thrombotic plaques were significantly more represented in men ($P = .013$). In particular, plaque ulceration was found more often in men. On the contrary, women had a higher degree of calcific nodules. Approximately 16% of women and 15% of men had vulnerable TCFA, whereas stable fibrocalcific plaque was evidently more frequent in women (38% compared to 26% of male patients).

Regarding the histologic plaque composition, the percentage of necrotic lipid core was higher in men ($P = .010$), and the same results were obtained regarding hemorrhagic area of the plaque ($P = .022$). Instead, no statistical difference emerged in the minimum cap thickness, but a trend placing men in the higher risk group was noted. No difference was found in calcium-lumen distance analysis or in the percentage of calcified area as well, with both genders presenting variable degrees of calcium in the plaque.

Subsequent analyses were performed to determine plaque inflammation features, and results are listed in Table III and Table IV. Relevant gender difference was recorded regarding the amount of inflammatory cells (macrophages and T-lymphocytes) present in the entire plaque ($P = .017$) and, in particular, in the cap ($P = .028$). The increase of inflammation observed in plaques from men was mainly due to increase of macrophage foam cells ($P = .009$).

Despite these apparent differences between men and women, multivariable analysis adjusted for cardiovascular risk factors, FHS, plaque features, stenosis severity, and symptom status showed that gender was no longer significantly associated with plaque inflammation features, thus suggesting that the above differences were largely driven by baseline factors, including stenosis severity and symptom status (Table IV).

DISCUSSION

This study was designed to test the hypothesis that carotid plaques differ between men and women. Women, all postmenopausal and not on hormone replacement therapy, as compared to men of the same age, had a lower prevalence of thrombotic plaques, and a smaller area of necrotic core and hemorrhage extension. Moreover, inflammatory features were less pronounced, thus confirming

the presence of gender-related differences, even if such differences were apparent only at bivariate analyses, and were no longer significant at multivariable analyses adjusting for other baseline variables, including symptom status and stenosis severity.

Gender differences in coronary vs carotid arteries. Gender difference in CVD is now widely accepted. Sex hormones seem to play a fundamental protective role in women through widespread actions, affecting endothelial function, lipid homeostasis, and cardiovascular risk factor reduction.[18-21] Moreover, some authors claim that estrogens might have plaque stabilization properties and effects on inflammatory status.[22,23] Previous histologic studies have demonstrated that in earlier stages of CAD, men presented more severe atheroma burden, and more diffuse endothelial dysfunction.[11,24] This difference seemed to decline over time, as atherosclerotic coronary plaques in postmenopausal women were shown to be similar to those of men and differed from those of women of childbearing age.[22]

Thus, estrogen role on coronary endothelium is not clearly defined yet. Trials on hormone replacement therapy have yielded contrasting results, without the clear cardiovascular benefit that was initially expected.[25] This has led many authors to speculate a possible age-dependent effect of estrogens, which reduces inflammation in younger age, while having opposite effects in older women.[15,26] However, similar results have not been reported on carotid arteries. On the contrary, estrogens seem to have mainly stabilizing and protective properties.[16,27,28] A recent ultrasound scan analysis recruiting over 1600 patients has documented significant lower plaque burden in women. The authors speculated that estrogens might act not only on risk factor reduction, but also directly on plaque morphology and arterial remodeling.[23] Subsequent trial comparing plaque features by means of histologic analysis or magnetic resonance imaging reported similar findings (ie, more inflammatory and high-risk features in men compared to women).[28-30] Thus, current evidence points toward a lasting protective effect of sex hormones in women in carotid arteries, slightly different from what has been reported on coronary arteries.

Gender differences in inflammatory features. Atherosclerotic plaque growth is a complex process. Plaques differ one another, with some of them leading to fatal events, whereas others remain stable and silent for many years.[12] Clinicopathological studies have identified a wide spectrum of alterations involving plaque surface, but eventually rupture of the fibrous cap is the triggering event for intravessel thrombosis and subsequent clinical events.[31-34] Thus, the vulnerable and rupture-prone plaque presents high fat content, high density of inflammatory features, thin fibrous cap, and low collagen and smooth muscle cells.[16,35,36]

Estrogens play a fundamental role on most aspects of plaque growth, conferring a cardiovascular advantage in women, at least in younger age.[37] Our results further confirm these findings, correlating gender difference with vulnerable plaque features. Our population was substantially similar regarding major baseline characteristics and overall number of risk factors, symptomatic status, and statin therapy. Moreover, our patients had no significant difference in plaque location among men and women. However, plaque features were significantly different.

Table IV. Plaque inflammation features at multivariable analysis[a]

	R^2	*Regression coefficient (95% CI)*	P *value*
Plaque inflammation (CD68 and CD3 positive cells in the plaque/mm^2)	2.4%	3.6 (−2.8 to 10.1)	.268
Cap inflammation (CD68 and CD3 positive cells in the cap/mm^2)	2.8%	−2.3 (−10.3 to 5.8)	.582
Foam cells (CD68 positive) in the cap/mm^2	2.3%	−0.48 (−7.5 to 6.6)	.133
T-lymphocytes (CD3 positive) in the cap/mm^2	0.4%	−2.4 (−5.4 to 0.7)	.124

CI, Confidence interval; *FHS,* Framingham Heart Score.
[a]Adjusting for all variables included in Tables I to II and associated at bivariate analyses with gender with $P < .10$: smoking status, hypercholesterolemia, hypertension, FHS, plaque classification, thrombotic plaque, percentage area of necrotic lipid core, hemorrhage extension, plus stenosis severity and symptom status. R^2 was computed using a gender as the only independent variable; female gender was coded as 2, and male gender as 1.

First of all, plaques in men seemed more complex, with higher rates of erosion, ulceration, and subsequent healing. On the contrary, women had higher rates of stable fibrocalcific plaques. Furthermore, thrombus burden, hemorrhagic areas, and necrotic lipid core were significantly higher in men. Distinctive inflammatory features,[38,39] represented by concentration of foam cells or lymphocytes in the cap were significantly lower in women.

This further supports previous findings, suggesting that in women, sex hormones play a protective role, maybe through plaque stabilization. Moreover, because all women were postmenopausal, the protective effect of estrogen on the carotid vascular bed might linger longer than in the coronary artery.

A recent systematic review has investigated outcomes in men and women after CEA, focusing on causal gender-related factors.[40] As expected, only a few trials were available addressing this topic. Plaque morphology was suggested as a gender-specific characteristic influencing outcomes after CEA, and in line with our findings, women's plaques were reported to have more stable characteristics than men's. Thus, the difference between men and women should not be forgotten even when planning treatment strategy, as gender-related characteristics seem to be related to clinical outcome.

Further studies are required to appraise in detail the implications of our study findings on patient management. However, we may speculate that gender, together with

other very important patient and lesion factors (such as symptom status and stenosis severity), should be taken into account for medical decision-making and risk-stratification. For instance, women and/or those with recent neurologic symptoms might benefit from high-dose preoperative statin therapy or could be considered potentially more suitable for surgical rather than endovascular therapy.

Limitations. Our study was not designed to test causal relationships or clinical implication of sex-related differences, or to evaluate estrogen levels in our population, thus remaining a descriptive and hypothesis-generating work. Moreover, it is still unclear how estrogen protection acts on the vascular bed, and how long this protection lasts. Therefore, gender-related differences are still far from being fully explained. Notably, our cases were all submitted to surgery after 30 days from symptoms onset. If we use a 30-day cutoff (instead of 120-day cutoff) to distinguish asymptomatic from symptomatic patients, all symptomatic plaques can be now be considered asymptomatic. Thus, the histomorphologic analysis hereby provided would yield the exact same results. We also considered in the group of thrombotic plaques those with organized thrombus. In this latter case, we considered the event of plaque thrombosis unrelated to the time of occurrence. Therefore, we did not underestimate the most important morphologic feature related to a clinical event. Finally, we did not perform systemic biomarker screening or noninvasive imaging to characterize high-risk plaque morphology because it was out of the scope of the present histopathology study. However, pathology may still be considered the gold standard for plaque characteristics of vulnerability.

CONCLUSIONS

Carotid plaques seem significantly different in women and men, but the main drivers of such pathologic differences are baseline feature, including stenosis severity and symptom status.

AUTHOR CONTRIBUTIONS

Conception and design: GS, AI, AM
Analysis and interpretation: SR, GBZ, MM
Data collection: FS, AI, AM
Writing the article: GS, SR, GBZ, AM
Critical revision of the article: GS, GBZ, MM, FS, AI, AM
Final approval of the article: GS, SR, GBZ, MM, FS, AI, AM
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