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Role of thrombocytosis in diagnosis of giant cell arteritis and differentiation of arteritic from non-arteritic anterior ischemic optic neuropathy

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PURPOSE. *To investigate the role of thrombocytosis in the diagnosis of giant cell arteritis (GCA), and differentiation of arteritic (A-AION) from non-arteritic (NA-AION) anterior ischemic optic neuropathy; and comparison of the sensitivity and specificity of platelet count to that of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and some other hematologic variables in the diagnosis of GCA.*

METHODS. *This retrospective study is based on 121 temporal artery biopsy confirmed GCA patients and 287 patients with NA-AION seen in our clinic. For inclusion in this study, all GCA patients, at their initial visit, prior to the initiation of corticosteroid therapy, must have had ESR (Westergren), platelet count and complete blood count, and temporal artery biopsy. From 1985 onwards CRP estimation was done. For inclusion in this study, all NA-AION patients at the initial visit must have undergone evaluation similar to that described above for GCA, except for temporal artery biopsy. Wilcoxon rank-sum test and the two-sample t-test were used to compare hematologic variables between GCA patients with and without visual loss, between those with and without systemic symptoms, and also between GCA and NA-AION patients. Pearson correlation coefficient was computed to measure the association of platelet counts and the other hematologic variables with ESR. Receiver operating characteristic (ROC) curves were constructed for ESR, CRP, platelet count, combinations of ESR and platelet count, and CRP and platelet count, hemoglobin, hematocrit, and white blood cell (WBC) count and the area under the curve (AUC) were compared.*

RESULTS. *Comparison of ESR, CRP, and hematologic variables of GCA patients and of A-AION with the NA-AION group, showed significantly ($p < 0.0001$) higher median levels of ESR, CRP, platelet count, and WBC count and lower levels of hemoglobin and hematocrit in the GCA patients and A-AION than in NA-AION. Comparing AUC of the ROC curve between ESR and platelet count, ESR was a better predictor of GCA compared to platelet count (AUC of 0.946 vs. 0.834). There was a slight improvement in prediction of GCA using the combination of ESR and platelet count (AUC=0.953). The other hematologic variables had an AUC that was smaller than platelet count (0.854 for hemoglobin; 0.841 for hematocrit), with WBC being the least predictive of GCA (AUC=0.666). The AUC of the ROC curve for CRP was 0.978. There was no improvement in prediction of GCA using platelet count in combination with CRP (AUC=0.976).*

CONCLUSIONS. *Patients with GCA had significantly ($p < 0.0001$) higher values of platelet count,*

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ESR, CRP and WBC but lower values for hemoglobin and hematocrit compared to the NA-AION group. Predictive ability of an elevated platelet count did not surpass elevated ESR or CRP as a diagnostic marker for GCA. Thrombocytosis may complement ESR. Hemoglobin, hematocrit and WBC were much less predictive of GCA. Elevated CRP had a greater predictive ability for GCA compared to ESR or the other hematologic parameters; thrombocytosis in combination with CRP did not yield an improvement in prediction of GCA. (Eur J Ophthalmol 2004; 14: 245-57)

KEY WORDS. *Anterior ischemic optic neuropathy, Erythrocyte sedimentation rate, Giant cell arteritis, Platelets, Temporal arteritis, Thrombocytosis*

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INTRODUCTION

Giant cell arteritis (GCA) is a systemic inflammatory vasculitis of uncertain etiology, which usually affects medium to large-sized arteries, in individuals aged greater than 50 years, and is often heralded by systemic symptoms including jaw claudication, neck pain, anorexia, weight loss, malaise, myalgia, headache, scalp tenderness, and fever (1). However, in occult GCA visual loss occurs without any systemic symptoms and that has been reported in 21% of GCA cases with visual loss (2). Kearns (3) rightly stressed that GCA "ranks as the prime medical emergency in ophthalmology, there being no other disease in which the prevention of blindness depends so much on prompt recognition and early treatment." In view of that, early diagnosis and start of steroid therapy is vital. For its early diagnosis, it is helpful to have as many diagnostic parameters of GCA as possible.

Apart from systemic symptoms, there are a number of proven hematologic tests used in the diagnosis of GCA including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (1). These are non-specific acute phase reactants, which are usually elevated at the time of diagnosis, and normalize (or decrease) with corticosteroid therapy.

In 1963 Olhagen (4) first reported thrombocytosis in 7 of his 12 GCA patients. Since then several reports of thrombocytosis in GCA have appeared in the literature (5-21), and Table I summarizes the major reports in the English language literature. These studies have suggested a role for estimation of platelet count in diagnosis and management of GCA because a decrease in platelet count with steroid therapy has also been reported. Some studies have linked thrombocytosis to a higher risk of ischemic complications in GCA (11, 12, 16, 20, 22, 23), while others did not find this relationship (8, 19, 24).

In our retrospective study, we investigated the role of thrombocytosis in the diagnosis of GCA, and differentiation of arteritic (A-AION) from non-arteritic (NA-AION) anterior ischemic optic neuropathy. We also compared the sensitivity and specificity of platelet count to that of ESR, CRP and some other hematologic variables in the diagnosis of GCA.

Design: Observational case series.

MATERIALS AND METHODS

This retrospective study was conducted in two groups of patients:

I. GCA patients with or without visual loss

The data for this study came from 121 GCA patients, seen in our clinic at the Tertiary Care University of Iowa Hospitals and Clinics from 1973 and who fulfilled our criteria of inclusion and exclusion for this study. There was no referral bias in these GCA patients because they were either referred to our department by other departments of our multi-specialty University Hospitals and Clinics (all temporal artery

TABLE I - SUMMARY OF REPORTS OF THROMBOCYTOSIS IN GCA, BASED ON LARGE SERIES

Author(s)	Patients (number)	Mean age (yrs)	Visual loss in (patients)	ESR Initial (mean) (mm/hr)	Percent of patients with Thrombocytosis ($x10^3/\mu l$)	Initial platelet count in $x10^3/\mu l$ (mean)	Temporal artery biopsy positive for GCA in
Malmvall et al (5)	68	69	8 (reversible)	88	35% (> 350)	338	42
Bengtsson (11)	80*	70*	NA	NA	54% (>350)	349	50*
De Keyser et al (12)	56	76	13	96 in patients with ischemia; 91 in without ischemia	37% (> 400)	475 in patients with ischemia; 338 in without	NA
Price et al (13)	10	NA	NA	72	NA	526	10
Gonzalez-Gay et al (15)	108 GCA = 63 GCA+PMR = 45	76 74	Permanent in 17 Transient in 13	GCA = 97 GCA+PMR = 91	NA	GCA = 413 GCA + PMR = 429	108
Lincoff et al (16)	19	75–men (12) 73–women(7)	Permanent in 10 Transient in 2	74	68% (>400)	477	19
Vrij et al (18)	19	72 (median)	NA	82	NA	507	19
Gonzalez – Alegre et al (19)	34	72	14 patients	98	44% (> 400)	379	18
Liozon et al.20	174	75	48	90	50% (> 400)	419	147
Foroozan et al (21)	47	78	NA	82	57% (>400)	433	47

* = From a total of 117 patients diagnosed as having GCA, platelet study performed in 80 patients. Author gives no demographic information on the latter group. Reported 62% of 117 had positive biopsy; hence extrapolating positive biopsy in 62% of 80 would be 50.
FUO = Fever of unknown origin. NA = Not available PMR = Polymyalgia rheumatica

biopsies for GCA for the entire medical center are performed in our department), or by outside ophthalmologists and physicians or self-referred for consultation.

At the initial visit, all patients were questioned in detail on the ocular and systemic signs and symptoms of GCA and other systemic disorders. All patients had detailed ophthalmic evaluation including Snellen visual acuity and visual field testing with a Goldmann perimeter, external and slit-lamp examination of the anterior segment, lens and vitreous, intraocular pressure measurement, and direct and indirect ophthalmoscopy. Patients with visual disturbance also had fluorescein fundus angiography. At their initial visit in our clinic and prior to the initiation of corticosteroid therapy, all patients had, on an emergency basis, estimation of ESR (Westergren), and from 1985 onwards CRP (initially, from 1985 till about 1990 CRP testing was not done regularly, because of limited facilities, but after that it was done in every patient), so that we had the results available within 1 to 1 1/2 hours; also most of the patients had a complete blood count done. All patients had temporal artery biopsy done as soon as convenient, to confirm the diagnosis.

For inclusion in the study, all patients must have had: a) diagnosis of GCA confirmed by temporal artery biopsy; b) ESR, platelets and complete blood count done before initiation of corticosteroid therapy; and c) must not have had any other evident concomitant systemic disease that could have influenced the blood tests. Although not an inclusion criterion, CRP data, when available before initiation of corticosteroid therapy, was also included in this study. All patients who were started on steroid therapy by the referring physicians, based on ESR testing only, without doing complete blood count, were excluded. These exclusion criteria disqualified many of our GCA patients for the study.

All patients were initially treated with high dose corticosteroid therapy using a treatment regimen described in detail elsewhere (25-27). In all patients, after the initiation of corticosteroid therapy and during follow-up, ESR and CRP were evaluated serially at each visit; however, complete blood count was not repeated serially so that, unlike ESR and CRP, we do not have information on the response of thrombocytosis and other hematologic variables to steroid therapy.

II. Non-arteritic anterior ischemic optic neuropathy patients

This group was composed of 287 patients. All were seen in our Ocular Vascular Clinic and consisted of two group: a) patients who were specifically investigated for hematologic and systemic abnormalities in a previous study on NA-AION (28) and had complete blood count done as a part of that study; b) in addition, we also included in the present study a random group of NA-AION patients seen in our clinic since the completion of the above study (28) who had the hematologic tests being evaluated in this study. Since the GCA patients were all more than 53 years old, only those NA-AION patients who were 50 years or older at initial diagnosis were included. The diagnosis of NA-AION was based upon the following: a) history of sudden visual loss, usually discovered on waking from sleep; b) presence of optic disc edema initially and within 2-3 months disc pallor; c) optic disc related visual field defect; and d) no evidence at initial visit or follow-up of neurologic, systemic (including GCA), or ocular disease that could be responsible for the visual loss or optic disc changes. At the initial visit, all NA-AION patients underwent evaluation similar to that described above for GCA, except for temporal artery biopsy; however, temporal artery biopsy was performed in cases where ESR, CRP and/or systemic signs and symptoms were suggestive of GCA, and that was found to be negative for GCA.

For inclusion in the study, all patients must have had: a) definite diagnosis of NA-AION (28); b) ESR, platelet and complete blood count done before initiation of corticosteroid therapy (where that therapy was given); and c) must not have had any other evident concomitant systemic disease that could have influenced the blood tests. Although not an inclusion criterion, CRP data, when available before initiation of corticosteroid therapy (where that therapy was given), was also included in this study.

Normal values for various hematologic variables

The normal values for ESR (in mm/hour Westergren) was based on cut-off points that we had defined in our previous study (1) based on 749 normal subjects [men: 17.3 ± 0.18 (age), women: 22.1 ± 0.18 (age)]. The normal values in hematology laboratory of our medical center have all along been for: 1) platelet count 150-400 x 10^3/µl; 2) CRP ≤ 0.5 mg/dl (1); 3) hemoglobin 13.2 - 17.7 G/dl for men and 11.9 - 15.5 G/dl for women; 4) white blood cell (WBC) count 3.7 - 10.5 x 10^3/µl; and 5) hematocrit 40-52% in men and 35-47% in women. Therefore, in this study, thrombocytosis was defined as a platelet count > 400 x 10^3/µl.

Statistical analysis

Hematologic variables were compared between GCA patients with and without visual loss using either the Wilcoxon rank-sum test or the two-sample t-test. These variables were also compared between those with and without systemic symptoms using the same tests. P-values were adjusted using Bonferroni's method to account for the number of variables that were compared. Pearson correlation coefficient was computed to measure the association of platelet and the other hematologic variables with ESR and CRP. The Wilcoxon rank-sum test was also used to compare ESR, CRP, and the hematologic variables between patients with GCA and the control group of non-arteritic AION. Logistic regression model was fitted with either ESR, platelet count, or both ESR and platelet count as independent variables. The probability of having GCA estimated from the fitted logistic regression was used to construct the receiver operating characteristic (ROC) curves for ESR, platelet count, combination of ESR and platelet count with the sensitivity and specificity values calculated for various probability cut-off points. This analysis was also performed for hematocrit, hemoglobin, and WBC count. The area under the curve (AUC) of the ROC curve was computed for each of these models to measure how well they predicted GCA. A similar analysis was also done for CRP, using the subgroup of patients that had presteroid therapy CRP measured (71 GCA and 103 non-arteritic AION). In addition, sensitivity, specificity, false

positive, and false negative rates for diagnosis of GCA relative to the control group were computed for ESR, platelet count, CRP and the other hematologic variables using the normal values described above as cut-off points. The upper limit of our hematology laboratory normal range was used as the cut-off for platelet count (400 X 10^3/µl) and WBC (10.5 X 10^3 /µl), and the lower limit of our laboratory normal range was used for hemoglobin and hematocrit (13.2 G/dl and 40% in men, respectively, and 11.9 G/dl and 35% in women, respectively).

RESULTS

Of the 121 GCA patients that had both ESR and platelet count measured, 70 (57.9%) patients had visual loss (Tab. II). The causes of vision loss included A-AION (52 patients), central retinal artery occlusion (12 patients), cilioretinal artery occlusion (5 patients), and posterior ischemic optic neuropathy (4 patients) – 3 patients had more than one cause of visual loss. Among patients with visual loss, there were 20 patients with a history of amaurosis fugax and 7 with diplopia. These visual disorders were seen alone or in different combinations. The gender and age distribution of these GCA patients and the 287 NA-AION patients are shown in Table II; gender and age distribution of these GCA patients is similar to that seen in our entire cohort of GCA patients in our clinic (1, 29).

Table III gives the comparison of the hematologic variables in GCA patients with and without visual loss. There was no significant difference in any of the levels of the hematologic variables between those with and without visual loss. We have shown in the same cohort of GCA patients in a recently published study (29) that those without visual loss had significantly higher ESR than those with visual loss (median 99 vs 84 mm/Hr), but no significant difference was found between the two groups for CRP (median 4.6 vs 4.5 mg/dl).

TABLE II - DEMOGRAPHIC CHARACTERISTICS

Study Group	n	Gender (% women)	Age at onset Mean (SD)	Age at onset Range
GCA	121	88 (72.7%)	75.3 (7.7)	53.4-93.4
No visual loss	51	39 (76.5%)	72.7 (7.3)	53.4-83.6
With visual loss	70	49 (70.0%)	77.1 (7.4)	56.0-93.4
With AION	52	37 (71.2%)	78.1 (6.5)	61.2-93.4
Non-arteritic AION	287	119 (41.5%)	64.8 (7.9)	50.2-91.6

TABLE III - COMPARISON OF INITIAL HEMATOLOGIC VARIABLES IN GCA PATIENTS WITH AND WITHOUT VISUAL LOSS

Variable	No visual loss n	No visual loss Median (IQR) or mean±SD	With visual loss n	With visual loss Median (IQR) or mean±SD	No visual loss vs. with visual loss p-value**
Platelets (10^3/µl)	51	425 (320-478)	70	406 (300-528)	1.0
WBC (10^3/µl)	51	9.0 (7.7-11.0)	70	8.8 (7.9-10.8)	1.0
Hb (G/dl)	51	11.9±1.5	70	12.5±1.9	0.412
HCT* (%)	44	36.7±4.5	64	37.7±4.9	1.0

IQR = Interquartile range = 25th – 75th percentile; Hb = Hemoglobin; HCT = Hematocrit; WBC = White blood cell; * = Missing data for HCT in 7 patients with no visual loss and 6 patients with visual loss; ** Bonferroni adjusted p-value

TABLE IV - COMPARISON OF INITIAL HEMATOLOGIC VARIABLES IN GCA PATIENTS WITH AND WITHOUT GENERAL SYSTEMIC SYMPTOMS OF GCA

Variable	Without systemic symptoms of GCA (n=17) Median (IQR) or mean±SD	With systemic symptoms of GCA (n=104) Median (IQR) or mean±SD	Without vs. with systemic symptoms p-value**
Platelets (10^3/µl)	332 (232-486)	425 (327-507)	0.204
WBC (10^3/µl)	7.3 (6.2-8.9)	9.0 (8.0-11.0)	0.023
Hb (G/dl)	13.2±1.4	12.1±1.8	0.070
HCT* (%)	(n=16) 39.9±3.9	(n=92) 36.9±4.7	0.071

IQR = Interquartile range = 25th – 75th percentile; Hb = Hemoglobin; HCT = Hematocrit; WBC = White blood cell; * = Missing data for Hct in 1 patient with no systemic symptom and 12 patients with systemic symptoms; ** Bonferroni adjusted p-value

We compared hematologic variables between GCA patients with and without (i.e. occult GCA (2)) general systemic symptoms of GCA (Tab. IV). The patients with systemic symptoms had a higher median WBC count (p=0.023) and a lower mean hemoglobin (p=0.070) and mean hematocrit (p=0.071) than those without systemic symptoms. There was no significant difference in median platelet count between those with and those without systemic symptoms (p=0.204). In our study (2) on occult GCA, we have shown in the same cohort of GCA patients that those with systemic symptoms had a significantly (p<0.0001) higher ESR than those without systemic symptoms (median 88 vs 52 mm/Hr) and this was also true (p= 0.013) of CRP (median 5.9 vs 2.0 mg/dl).

Examination of the relationship between the hematocrit and ESR showed a significant negative correlation (r = –0.50; 95% CI: –0.35, –0.63; p<0.0001) (Fig. 1). There was also a negative correlation between ESR and hemoglobin (r= –0.46; 95% CI: –0.31, –0.59; p<0.0001). A lower degree of correlation was seen between platelet count and ESR (r= 0.33; 95% CI: 0.16, 0.48; p=0.0003) (Fig. 2), with a non-significant correlation between ESR and WBC (r= 0.15; 95% CI: -0.03, 0.342; p=0.104).

For the 71 GCA patients with CRP, CRP did not show a significant correlation with platelets (r=0.04; 95% CI: –0.20, 0.27; p=0.757), hematocrit (r=–0.22; 95% CI: –0.44, 0.04; p=0.094), hemoglobin (r=–0.13; 95% CI: –0.36, 0.10; p=0.269), and WBC (r=–0.01; 95% CI: –0.25, 0.22; p=0.913).

Comparison of ESR, CRP, and hematologic variables

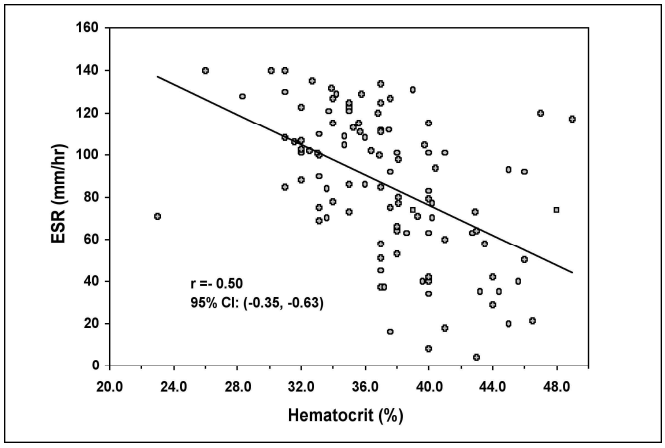

Fig. 1 - *This scatter plot shows the relationship between the hematocrit and ESR in GCA. There was a significant negative correlation between the two (r = -0.50; 95% CI: -0.35, -0.63; p<0.0001).*

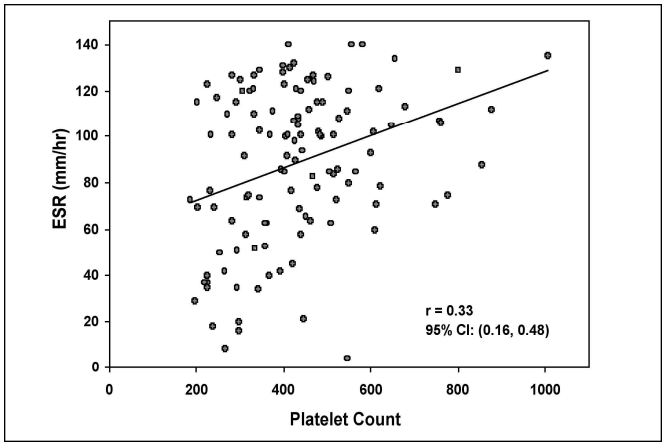

Fig. 2 - *This scatter plot shows the relationship between platelet count (10^3/µl)) and ESR in GCA. There was a weak correlation between the two (r=0.33; 95% CI: 0.16, 0.48; p=0.0003).*

of GCA patients and of A-AION with the NA-AION group, showed significantly ($p < 0.0001$) higher median levels of ESR, CRP, platelet count, and WBC count and lower levels of hemoglobin and hematocrit in the GCA patients and A-AION than in NA-AION (Tab. V).

The ROC curves for predicting GCA using ESR, platelet count, hemoglobin, hematocrit, WBC count, and the combination of ESR and platelet count are shown in Figure 3a. ESR (AUC=0.946) was a better predictor of GCA compared to platelet count (AUC=0.834), hemoglobin (AUC=0.854) and hematocrit (AUC=0.841). The combination of ESR and platelet count resulted in a slight improvement in predictive ability (AUC=0.953) over ESR alone. WBC was least predictive of GCA (AUC=0.666).

To be able to compare the predictive ability of CRP with ESR and platelet, the ROC analysis was performed on a subgroup of patients that had CRP measured (71 GCA and 103 N-AION) (Fig. 3b). CRP(AUC=0.978) was a better predictor of GCA than ESR (AUC=0.909) and platelet count (AUC=0.816), as well as the combination ESR and platelet count (AUC=0.920). The combination of platelet count with CRP (AUC=0.976) did not improve predictive ability compared to CRP alone.

The combinations of sensitivity and specificity that were used to construct the ROC curve for the ESR-platelet count combination were examined to select a cut-off with desirable levels of false negative and false positive rates. Since missing a diagnosis of GCA could result in visual loss in one or both eyes, we would want to have the lowest possible false negative rate while keeping the false positive rate at an acceptable level. Figure 4 shows 3 cut-off lines, A, B, and C, that correspond to the lowest false negative rate (4.9%, 5.6% and 8.9% respectively) with the false positive rate no higher than 24.5%, 14.6%, and 9.6%, respectively. The points that fall in the region to the right or above the line are predicted to have GCA and the points in the region to the left or below the line are predicted not to have GCA. For example, for line B in Figure 4, sensitivity is 86.8%, specificity is 93.7%, with a false negative rate of 5.6% and false positive rate of 14.6%.

Sensitivity, specificity, false negative, and false positive rates for diagnosis of GCA using our normal laboratory values for ESR, CRP, platelets, WBC count, hemoglobin, and hematocrit are shown in Table VI. This shows that false negative rate was lowest with CRP (1.3%) and ESR (2.9%) compared with the other hematologic tests (platelet count 15.8%, hemoglobin 26.3%, hematocrit 26.6%, and WBC 34.1%).

TABLE V - INITIAL ESR, CRP, AND HEMATOLOGIC VARIABLES IN GCA AND NON-ARTERITIC AION

Variable	GCA (n=121) Median (IQR)	Arteritic AION (n=52) Median (IQR)	Non-arteritic AION (n=287) Median (IQR)
ESR (mm/hr)	98 (66-115)	92.5 (69.5-110.5)	14* (7-268)
CRP (mg/dl)	(n=71) 8.5 (4.1-17.1)	(n=22) 9.5 (5.0-13.4)	(n=103) 0.4* (0.1-0.5)
Platelets (10^3/µl)	421 (313-504)	433.5 (318-536.5)	263* (222-309)
WBC (10^3/µl)	8.8 (7.8-10.8)	8.9 (7.9-10.9)	(n=196) 7.4* (6.2-9.1)
Hb (G/dl)	12.2 (11.0-13.3)	12.0 (10.8-13.3)	(n=177) 14.7* (13.6-16.0)
Hct (%)	(n=108) 37 (34-40.0)	(n=48) 37 (33.1-40.0)	(n=196) 44* (41.0-47.0)

IQR = Interquartile range = 25th – 75th percentile; CRP = C-reactive protein (Estimated from 1985 onwards); HCT = Hematocrit; Hb= Hemoglobin; WBC = White blood cell; * = p-value<0.0001 compared to GCA and arteritic AION

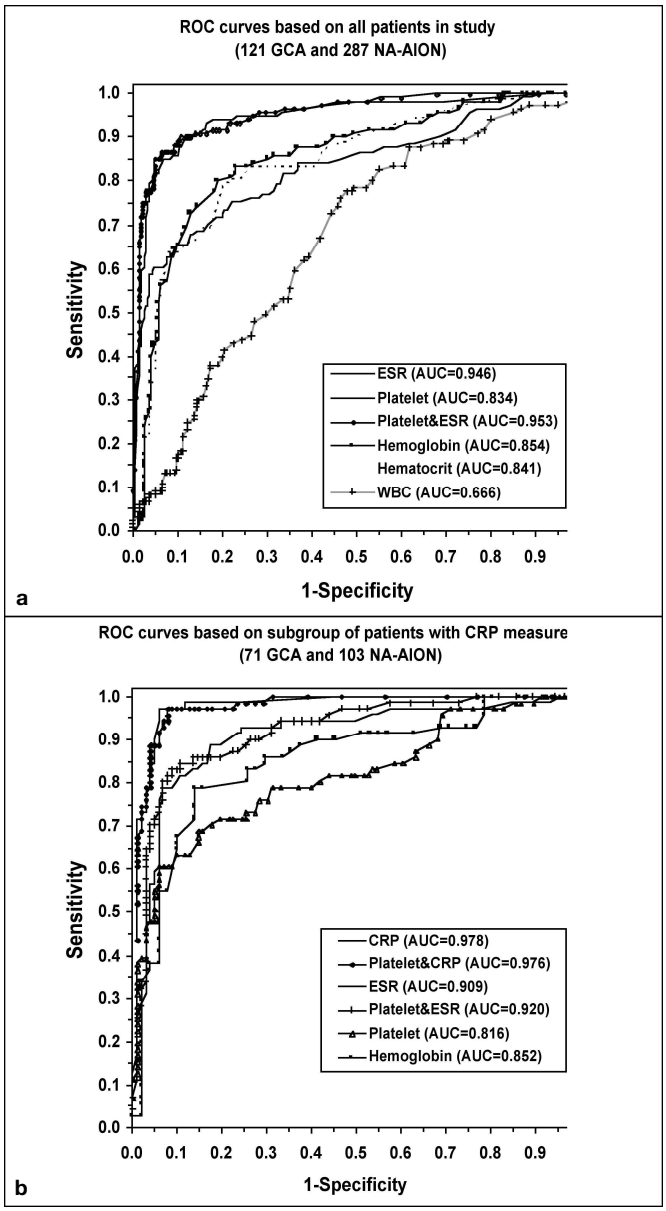

Fig. 3 - *Receiver Operating Characteristic (ROC) Curves for prediction of GCA from logistic regression analysis:*
a) *ROC curves based on all patients in study (121 GCA and 287 NA-AION), with ESR, platelet count, hemoglobin, hematocrit, WBC, or combination of ESR and platelet count as independent variables. Comparing area under the curve (AUC), ESR is a better predictor of GCA compared to the other hematologic variables. There is a small increase in AUC using platelet count in combination with ESR compared to ESR alone.*
b) *ROC curves based on a subgroup of patients with CRP measured (71 GCA and 103 NA-AION), with CRP, ESR, platelet count, hemoglobin, combination of ESR and platelet count, or combination of CRP and platelet count as independent variables. Comparing area under the curve (AUC), CRP is a better predictor of GCA compared to all other hematologic variables. There is no increase in AUC using platelet count in combination with CRP compared to CRP alone.*

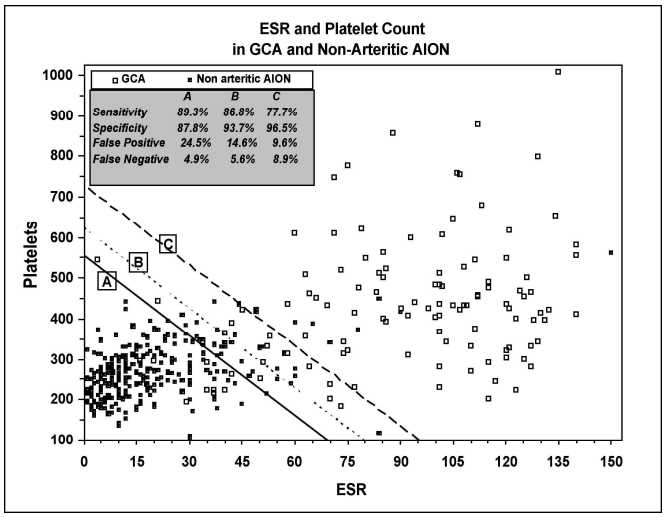

Fig. 4 - *Three selected cut-off lines for prediction of GCA status based on combination of ESR and platelet count. The cut-off lines, A, B, and C, correspond to the three lowest false negative rates with the false positive rates. The points that fall in the region to the right or above the line are predicted to have GCA and the points in the region to the left or below the line are predicted to not have GCA.*

DISCUSSION

Thrombocytosis in GCA

In our retrospective review of 121 patients with biopsy proven GCA, 57.0% had thrombocytosis, defined by hematology laboratory of our University Hospitals and Clinics, as a serum platelet count > 400 x 10^3/µl. Table I summarizes the major studies from the literature reporting thrombocytosis in GCA, its prevalence, the cut-off values used to define thrombocytosis and other relevant information. This shows marked disparities among various studies about the prevalence rate of thrombocytosis, the cut-off values used to define thrombocytosis, as well as the criteria used to diagnose GCA. For example, there are several studies (5, 6, 11, 12, 19, 20) in which a positive temporal artery biopsy was not an inclusion criterion for the diagnosis of GCA (Tab. I); in our series all the 121 patients had temporal artery biopsy-proven GCA.

The finding of an elevated platelet count in GCA has been described as reactive thrombocytosis and attributed to the systemic inflammation present with this disorder (6, 16). In our study as well as in most other studies (5, 6, 9, 12-22) platelet count was evaluated among

TABLE VI - SENSITIVITY AND SPECIFICITY WITH EXACT 95% CONFIDENCE INTERVAL OF ESR AND HEMATOLOGIC VARIABLES FOR DIAGNOSIS OF GCA VERSUS NON-GCA

Criteria		Sensitivity	Specificity	False negative	False positive
ESR*	n	114/121	231/287	7/238	56/170
	%	94.2%	80.5%	2.9%	32.9%
	95% CI	(88.4%, 97.6%)	(75.4%, 84.9%)	(1.2%, 6.0%)	(25.9%, 40.6%)
CRP 0.5 mg/dl	n	70/71	78/103	1/79	25/95
	%	98.6%	75.7%	1.3%	26.3%
	95% CI	(92.4%, 99.9%)	(66.3%, 83.6%)	(0.03%, 6.9%)	(17.8%, 36.4%)
Platelet count	n	69/121	277/287	52/329	10/79
400 X 10^3/µL	%	57.0%	96.5%	15.8%	12.7%
	95% CI	(47.7%, 66.0%)	(93.7%, 98.3%)	(12.0%, 20.2%)	(6.2%, 22.1%)
WBC 10.5 X 10^3/µL	n	34/121	168/196	87/255	28/62
	%	28.1%	85.7%	34.1%	45.2%
	95% CI	(20.3%, 37.0%)	(80.0%, 90.3%)	(28.3%, 40.3%)	(32.5%, 58.3%)
Hb**	n	56/121	182/196	65/247	14/70
	%	46.3%	92.9%	26.3%	20.0%
	95% CI	(37.2%, 55.6%)	(88.3%, 96.0%)	(20.9%, 32.3%)	(11.4%, 31.3%)
HCT***	n	43/108	179/196	65/244	17/60
	%	39.8%	91.3%	26.6%	28.3%
	95% CI	(30.5%, 49.7%)	(86.5%, 94.9%)	(21.2%, 32.7%)	(17.5%, 41.4%)

HCT = Hematocrit; Hb = Hemoglobin; WBC = White blood cell; * = 17.3+0.18(Age) for males and 22.1+0.18 (Age) for females (1); ** = 13.2 X 10^3/µl for males and 11.9 for females; *** = 40% for males and 35% for females

GCA patients at the time of initial presentation, before the start of steroid therapy, as an acute phase reactant. Some authors have also studied the change in platelet count over time or in response to corticosteroid therapy among patients with GCA (6, 11, 14, 16, 18, 19). Lincoff et al (16) studied the platelet count in the year prior to diagnosis among 19 patients with biopsy-proven GCA, and described an "escalating thrombocytosis" among 13 patients; notably, all 13 patients showed a drop in their platelet count after treatment with corticosteroids, which has also been reported by most of the other studies in the literature.

There are reports in the literature claiming that GCA patients with systemic symptoms have higher platelet counts than those without systemic symptoms (9, 18). This difference was not observed when we compared GCA patients with and without systemic symptoms (Table IV).

Association between thrombocytosis in GCA and ischemic complications

The role of elevated platelet count and the possible association of thrombocytosis with ischemic complications has been debated in the literature (8, 11, 12, 15, 19, 20, 22-24). For example, De Keyser et al (12) reported a correlation between thrombocytosis and ischemic lesions because their group with ischemic complications (18 patients with visual loss, stroke and transient ischemic attack) had a significantly ($p<0.01$) higher prevalence of thrombocytosis and a higher median platelet count than the group without those ischemic complications (38 patients). Similarly Liozon et al (20) concluded that there was a correlation between increased risk of vision loss and higher platelet counts. However, a careful review of the data and statistical methods in the latter study revealed that in the analysis used to identify the independent risk factors

for permanent vision loss, there were 17 variables in the logistic regression model of 23 patients with permanent vision loss and 151 with no vision loss. In such an analysis, a general rule is to include no more than 1 independent variable per 10 subjects in the smaller of the two outcome groups to derive a model that is reliable (30). Therefore, Liozon et al's (20) analysis incorporated too many independent variables in the logistic regression model for the small sample size, and that resulted in a model that is over-fitted. Thus, the conclusions derived from their multiple logistic regression model may not be valid.

Those who believe in a possible relationship between thrombocytosis and ischemic lesions in GCA, have proposed various mechanisms to account for it. Bengtsson (11) speculated that the arteritic process may adversely affect the prostacyclin synthesis in the arterial wall, thereby disturbing the balance between prostacyclin and thromboxane A_2 release from the "activated platelets", a substance known to be a potent vasoconstrictor as well as a proaggregatory agent (31). Gibb et al (22), in one case of fatal basilar artery thrombosis and GCA, found high platelet count (566 x 10^3/µl), and concluded that ischemia could result from embolization of platelet clumps from inflamed intimal surfaces or by release of thromboxane A_2 by activated platelets producing platelet aggregation and vasoconstriction.

In contrast to that, other authors have found no such association between thrombocytosis and an increased risk of ischemic complications in GCA (19, 24) For example, Cid et al (24), in a study of 200 consecutive biopsy-proved GCA patients, on comparing patients with ischemic lesions (32 patients) versus those without ischemic lesions (168 patients), found no significant difference in platelet count between the two. Wu (32) found none of the 11 patients with reactive thrombocytosis had thrombotic or hemorrhagic complications. In our study of 121 GCA patients, we also found no significant difference in the mean platelet counts between GCA patients with vision loss (406 x 10^3/µl) and those without (425 x 10^3/µl) (Tab. III). It is relevant to point out that permanent visual loss, as a complication of biopsy-proved GCA, was much higher in our study than has been reported in other GCA studies dealing with thrombocytosis (5, 8, 9, 12, 15-17, 19-21, 24). Therefore, our study provides much more reliable information on this issue than previous studies.

The study by Kaiser et al (23) showed that it is the degree of intimal proliferation that plays a role in the development of ischemic lesions and not an embolic phenomenon. The lumen of arteries involved by GCA is usually reduced by severe thickening of the intima, and thrombus is often formed at the site of active inflammation. Our fluorescein fundus angiographic studies of GCA patients with A-AION (due to occlusion of the posterior ciliary artery), central retinal artery occlusion and cilioretinal artery occlusion indicate that visual loss is primarily due to occlusion of the involved artery by arteritis and associated thrombosis and not due to embolism (28, 33, 34) However, the possibility of detached microscopic clumps of platelets or other material from the surface of a freshly forming thrombus, before the thrombus completely occludes the common trunk of the posterior ciliary artery and central retinal artery (35), producing retinal cotton-wool spots (29) cannot be ruled out; on the other hand it is important to bear in mind that such transient microscopic emboli are almost invariably too small to cause occlusion of main ocular arteries and produce the devastating permanent visual loss of GCA. Thus, there is no convincing evidence that ischemic manifestations occur as a direct consequence of reactive thrombocytosis in GCA, particularly with the rather moderate increases in platelets seen in GCA patients.

As regards the role of aspirin or other platelet anti-aggregating agents to prevent visual loss in GCA, todate there are no studies in support of their efficacy to do that. Gonzales-Alegre et al (19) also found no evidence to support the idea of starting platelet aggregation inhibitors to prevent ischemic complications of GCA. In our study, because there was no significant difference in the platelet counts of patients with ocular ischemic complications compared to those without in GCA (Tab. III), treatment with aspirin or other platelet anti-aggregating agents to prevent visual loss in GCA may not be justified. It seems the faulty rationale for the use of aspirin in GCA to prevent ischemic complications stems from confusion between two very different types of thrombocytosis: reactive thrombocytosis (seen in GCA) and essential thrombocytosis (a chronic progressive myeloproliferative disorder of insidious onset). With essential thrombocytosis there is a high risk of thrombotic involvement of major vessels and the microcirculation (37), and aspirin is usually effective at relieving vasomotor and

microvascular occlusive symptoms, although there is only limited evidence that its use reduces the risk of larger vessel thrombosis even in those cases (34) Also there is no evidence that anticoagulants help to prevent blindness in GCA (8, 36).

Other hematologic abnormalities in GCA

It is well-established that GCA patients have anemia (5, 9, 21). Therefore we also compared median levels of other hematologic variables between our GCA and NA-AION patients. The former had a significantly ($p < 0.0001$) higher level of WBC count and lower levels of hemoglobin and hematocrit than the latter (Tab. V).

Role of thrombocytosis in differentiation of arteritic from non-arteritic AION

AION is a visually disabling disease common in the age group of persons developing GCA. A-AION (due to GCA) is a prime medical ophthalmic emergency, with a high risk of further visual loss in one or both eyes, which can be prevented by early diagnosis and intensive steroid therapy (26, 27). In contrast to that, we have no known treatment for NA-AION. Therefore, differentiation of A-AION from NA-AION is of primary clinical importance from the point of view of management of AION and prevention of blindness.

Price and Clearkin (13) compared platelet count in 10 A-AION patients (with biopsy proven GCA) to 7 NA-AION patients (with negative biopsy for GCA) and found "no overlap of values and a sharp cut-off point at 350 x 10^9/µl" between the A-AION and NA-AION groups. Lincoff et al (16) found abnormal platelet count (>400 x 10^3 µl) in 13 of 19 GCA patients, compared to none of the 30 NA-AION patients, none of the 26 optic neuritis patients, and 1 of 22 healthy age-matched controls ($p<0.001$). In a recent study, Foroozan et al (21) compared the mean ESR and platelet count between 47 temporal artery biopsy-positive GCA cases and 44 biopsy-negative patients. They found that the mean platelet count was significantly ($p<0.0001$) higher in the biopsy-positive group than in biopsy-negative group. The sensitivity (79%) of an elevated ESR was greater than that of elevated platelet count (57%); however, the specificity (91%), positive predictive value (87%), and negative predictive value (67%) favored an elevated platelet count over an elevated ESR. Based on their findings, the authors concluded that "an elevated platelet count greater than 400 x 10^3 /µl is a useful marker of a positive temporal artery biopsy". However, in their study the sensitivity of elevated platelet count was only 57%. Thus, if one did temporal artery biopsy only in those patients who had elevated platelets (>400 x 10^3/µl), 43% of the GCA patients would be missed, and that is an unacceptably high risk. Foroozan et al (21) found no significant difference in the mean ESR between the biopsy-positive and biopsy-negative groups which conflicts with the findings in other studies (1); they rightly attributed that discrepancy to the built in bias in their study design in that "an elevated ESR was an important factor that determined which patients underwent temporal artery biopsy" (21). That factor would also explain the finding of poorer positive (54%) and negative (55%) predictive values for ESR compared to those for platelet count. In sharp contrast to that, in our study the ESR and platelet count of the GCA and A-AION patients were significantly ($p<0.0001$) higher than those of the NA-AION patients (Tab. V).

Our study suggests that in the rare cases where the ESR and CRP may not be conclusive, thrombocytosis and other hematologic abnormalities (e.g., low hemoglobin, hematocrit) may be helpful in suspecting and diagnosing GCA and A-AION, although they may not, individually, add very much to the value of ESR and/or CRP. This is because GCA and A-AION patients had a significantly ($p<0.0001$) higher WBC count and lower hemoglobin and hematocrit levels than the NA-AION patients (Tab. V). In some patients with NA-AION in our study, although the ESR and /or CRP were elevated, the platelet count was within normal limits; that information can be a helpful clue in the differentiation of NA-AION from A-AION.

Our study has its strengths and limitations. Being a retrospective study it has some of the usual limitations involved in a retrospective study; however, most of the patients in this study were evaluated and treated as a part of planned prospective studies investigating various aspects of GCA in our clinic since 1973 (1, 2, 25-27, 29). The other limitation is that we did not have as many GCA patients with information on the initial CRP as for ESR and other hematologic variables; this was due to two factors: a) CRP testing was not started till 1985 and initially from 1985

till about 1990 CRP testing was not done regularly, because of limited facilities, and b) more importantly, our inclusion criterion excluded those patients who did not have CRP done by the referral physicians before they started steroid therapy. The strength of our study is that it is based on a large number of temporal artery biopsy confirmed GCA patients, and the largest number of AION patients ever studied to define hematologic parameters to differentiate A-AION from NA-AION, so that the data of this study provide firm information on this extremely important blinding disease.

CONCLUSIONS

Patients with GCA had significantly ($p<0.0001$) higher values for platelet count, ESR, and CRP as compared to the control group, yet there was no difference in the platelet counts among GCA patients with and without ischemic visual complications. The predictive ability of an elevated platelet count did not surpass elevated ESR or CRP as a diagnostic marker for GCA. Thrombocytosis may complement the ESR. Hemoglobin, hematocrit and WBC were much less predictive of GCA than ESR, CRP or thrombocytosis. Our study showed that elevated CRP has a greater predictive ability for GCA than ESR or the other hematologic parameters. Thrombocytosis in combination with CRP did not yield an improvement in prediction of GCA. In rare cases, however, where the ESR and CRP may not be conclusive, thrombocytosis and other hematologic abnormalities (e.g., low hemoglobin, hematocrit) may be helpful in suspecting and diagnosing GCA and A-AION, although individually they may not add much to the value of ESR and/or CRP. In view of that, we recommend that it is useful to do complete blood count in addition to ESR and CRP in patients suspected of having GCA and/or A-AION.

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REFERENCES

1. Hayreh SS, Podhajsky PA, Raman R, Zimmerman B. Giant cell arteritis: Validity and reliability of various diagnostic criteria. Am J Ophthalmol 1997; 123: 285-96.
2. Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: Ocular manifestations. Am J Ophthalmol 1998; 125: 521-6, 893.
3. Kearns TP. Collagen and rheumatic diseases: Ophthalmic aspects. In: Mausolf FA, editor. The Eye and Systemic Disease. St. Louis: Mosby, 1975: 105-18.
4. Olhagen B. Polymyalgia rheumatic: A form of senile arteritis? Acta Rheum Scand 1963; 9: 157-64.
5. Malmvall BE, Bengtsson BA. Giant cell arteritis: Clinical features and involvement of different organs. Scand J Rheumatol 1978; 7: 154-8.
6. Bergström AL, Bengtsson BA, Olsson LB, et al. Thrombokinetics in giant cell arteritis, with special reference to corticosteroid therapy. Ann Rheum Dis 1979; 38: 244-7.
7. Giordano M. Thrombocytosis in giant cell arteritis. Ann Rheum Dis 1980; 39: 298.
8. Calamia KT, Hunder GG. Clinical manifestations of giant-cell (temporal) arteritis. Clin Rheum Dis 1980; 6: 389-403.
9. Calamia KT, Hunder GG. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. Arthritis Rheum 1981; 24: 1414–8.
10. Riddle JM, Bluhm GB, Pitchford WC, et al. A comparative study of platelet reactivity in arthritis. Ann N Y Acad Sci 1981; 370: 22-9.
11. Bengtsson BA. Hematological observations in giant cell arteritis. Acta Med Scand 1982; Suppl 658: 44-7.
12. De Keyser J, De Klippel N, Ebinger G. Thrombocytosis and ischemic complications in giant cell arteritis. Br Med J 1991; 303: 825.
13. Price N, Clearkin LG. Thrombocytosis and giant cell arteritis. Lancet. 1994; 343: 672.
14. Krishna R, Kosmorsky GS. Implications of thrombocytosis in giant cell arteritis. Am J Ophthalmol 1997; 124: 103.

15. González-Gay MA, García–Porrua C, Vázquez–Caruncho M. Polymyalgia rheumatica in biopsy proven giant cell arteritis does not constitute a different subset but differs from isolated polymyalgia rheumatica. J Rheumatol 1998; 25: 1750-5.
16. Lincoff NS, Erlich PD, Brass LS. Thrombocytosis in temporal arteritis rising platelet counts: A red flag for giant cell arteritis. J Neuroophthalmol 2000; 20: 67-72.
17. Hu Z, Yang Q, Zheng S, et al. Temporal arteritis and fever: Report of a case and a clinical reanalysis of 360 Cases. Angiology 2000; 51: 953-8.
18. Vrij AA, Rijken J, van Wersch JWJ, Stockbrügger RW. Platelet factor 4 and ß-thromboglobulin in inflammatory bowel disease and giant cell arteritis. Eur J Clin Invest 2000; 30: 188-94.
19. Gonzales–Alegre P, Ruiz-Lopez AD, Abarca–Costalago M, Gonzalez-Santos P. Increment of the platelet count in temporal arteritis: Response to therapy and ischemic complications. Eur Neurol 2001;45:43-45.
20 Liozon E, Herrmann F, Ly K, et al. Risk factors for visual loss in giant cell (temporal) arteritis: A prospective study of 174 patients. Am J Med 2001; 111: 211-7.
21. Foroozan R, Danesh-Meyer H, Savino PJ, et al. Thrombocytosis in patients with biopsy-proven giant cell arteritis. Ophthalmology 2002; 109: 1267-71.
22. Gibb WRG, Urry PA, Lees AJ. Giant cell arteritis with spinal cord infarction and basilar artery thrombosis. J Neurol Neurosurg Psychiatry 1985; 48: 945-8.
23. Kaiser M, Weyand CM, Björnsson J, Goronzy JJ. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. Arthritis Rheum 1998; 41: 623-33.
24. Cid MC, Font C, Oristrell J, de la Sierra A, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum 1998; 41: 26-32.
25. Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis: Report of a large study and review of literature. Acta Ophthalmol Scand 2002; 80: 355-67.
26. Hayreh SS, Zimmerman B. Management of giant cell arteritis: Our 27-Year Clinical Study; New Light on Old Controversies. Ophthalmologica 2003; 217: 239-59.
27. Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology 2003; 110: 1204-15.
28. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with non-arteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1994; 118: 766-80.
29. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol 1998; 125: 509-20.
30. Harrell FE. Chapter 23: The LOGIST Procedure, SUGI Supplemental Library User's Guide, Version 5 Edition, SAS Institute Inc., Cary, NC, 1986; 269-93.
31. Moncada S, Vanse JR. Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. New Engl J Med 1979; 300: 1142-7.
32. Wu KK. Platelet hyperaggregability and thrombosis in patients with thrombocythemia. Ann Intern Med 1978; 88: 7-11.
33. Hayreh SS. Anterior ischaemic optic neuropathy II. Fundus on ophthalmoscopy and fluorescein angiography. Br J Ophthalmol 1974; 58: 964-80.
34. Hayreh SS. Anterior ischaemic optic neuropathy: Differentiation of arteritic from non-arteritic type and its management. Eye 1990; 4: 25-41.
35. Singh S, Hayreh SS, Dass R. The central artery of the retina I. Origin and course. Br J Ophthalmol 1960; 44: l93-2l2.
36. Russell RWR. Giant cell arteritis. QJM 1959; 28: 471-89.
37. Pearson TC. The risk of thrombosis in essential thrombocythemia and polycythemia vera. Semin Oncol 2002; 29 (Suppl): S16-21.

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