Epidemiological study of primary systemic vasculitides among adults in southern Spain and review of the main epidemiological studies

C. Romero-Gómez[1], J.A. Aguilar-García[1], M.D. García-de-Lucas[1], R. Cotos-Canca[1], J. Olalla-Sierra[1], J.J. García-Alegría[1], J. Hernández-Rodríguez[2]

[1]Department of Internal Medicine, Hospital Costa del Sol, Marbella, Spain; [2]Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Carlos Romero-Gómez, MD
Josefa A. Aguilar-García, MD
M. Dolores García-de-Lucas, MD
Rafael Cotos-Canca, MD
Julián Olalla-Sierra, MD
J. Javier García-Alegría, MD
José Hernández-Rodríguez, MD

The results of this study were partially presented at the 16th International Vasculitis and ANCA Workshop, Paris (France), April 2013.

Please address correspondence to:
José Hernández-Rodríguez, MD,
Department of Autoimmune Diseases,
Hospital Clínic,
Villarroel 170,
08036 Barcelona, Spain.
E-mail: jhernan@clinic.ub.es

Received on April 26, 2014; accepted in revised form on July 14, 2014.

Clin Exp Rheumatol 2015; 33 (Suppl. 89): S11-S18.

Key words: primary systemic vasculitis, vasculitis, epidemiology, incidence, prevalence

Funding: J. Hernández-Rodríguez was supported by the Ministerio de Economía y Competitividad of Spain (SAF 11/30073).

Competing interests: none declared.

.**ABSTRACT**

Objective. *To study the incidence and prevalence of primary systemic vasculitides (PSV) in the Costa del Sol region (southern Spain) and to compare the major epidemiological studies in PSV with the results obtained in our area.*

Methods. *Retrospective study including permanent residents ≥14 years (or older) diagnosed with PSV at the Hospital Costa del Sol (Marbella, Spain) between 1994 and 2010. Epidemiological data were collected and the annual incidence rate during the study period and the prevalence in 2010 were calculated per million population, except for GCA, which was estimated per 100,000 population >50 years.*

Results. *Seventy-four adult patients were diagnosed with PSV, representing an annual incidence of 15.8 (95%CI 12.2–19.4) patients/million population. These diagnoses included 29 (39.1%) giant cell arteritis (GCA), 5 (6.7%) Takayasu's arteritis (TA), 3 (4%) polyarteritis nodosa (PAN), 29 (39.1%) antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [10 (13.5%) granulomatosis with polyangiitis (GPA) (Wegener), 16 (21.6%) microscopic polyangiitis (MPA) and 3 (4%) eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss)], 7 (9.4%) IgA vasculitis (Henoch-Schönlein) (IgAV) and one (1.3%) cryobulinaemic vasculitis (CV). The annual incidence and 2010 prevalence for each of the PSV, respectively, were: GCA: 2.2/12.2; TA: 1.1/10.5; PAN: 0.6/2.6; AAV: 6.2/44.8 (GPA: 2.1/15.8; MPA: 3.4/23.8; EGPA: 0.6/5.3); IgAV: 1.5/7.9; and CV: 0.2/0.*

Conclusion. *The first epidemiological study of PSV in southern Spain corroborates their infrequency, with GCA and AAV as the PSV most often diagnosed. In southern Spain, the incidence and prevalence of PSV are lower than in northern Spain and in countries in the Northern Hemisphere.*

Introduction

Vasculitides are a heterogeneous group of disorders characterised by inflammation of the blood vessel walls. To date no diagnostic criteria have been yet established for primary systemic vasculitides (PSV), those considered of unknown aetiology (1, 2). The categorisations most often used are the 1990 vasculitis classification criteria of the American College of Rheumatology (ACR) (3), and the nomenclature and definitions established in the 1994 Chapel Hill consensus conference (CHCC) (North Carolina, USA) (1), which have been recently revised and updated at a new 2012 CHCC criteria (2).

Following the discovery and improvement of the determination of anti-neutrophil cytoplasmic antibodies (ANCA) in the 1990s, ANCA-associated vasculitides (AAV) were defined for the first time in 1994, at the first CHCC (1). Microscopic polyangiitis (MPA) was also distinguished from polyarteritis nodosa (PAN) in 1994 (1). Finally, at the 2012 CHCC, PSV were clearly differentiated from the secondary forms of vasculitis (2). This distinction has entailed important implications, including the new categorisation of vasculitis associated with hepatitis B virus (HBV), previously classified as PAN (by 1990 ACR classification criteria) (4), which has made (idiopathic) PAN even more uncommon than it was before the use of ANCA for the diagnosis of AAV (5, 6).

Epidemiological studies of PSV have revealed a low incidence and prevalence in the general population. Major studies in this respect have been conducted in

Europe (7-37), mainly in Scandinavian countries, the UK, Germany, France, Italy, Turkey and Spain, and the USA (38-40), as well as other geographic areas such as Israel, Peru, Australia, New Zealand, Japan and other Asian countries (41-49).

To date, epidemiological studies of PSV in Spain have been performed in northern areas (8, 11, 14, 15, 26-28), mainly northwestern Spain (8, 11, 14, 26-28). The present study analyses the epidemiology of PSV affecting adults in the western part of the Costa del Sol region (southern Spain). The results obtained are compared with those derived from the main epidemiological studies of PSV conducted to date.

Methods

Study population, catchment area and study period

This study considered adult patients with PSV diagnosed in the West Costa del Sol Health District in the province of Málaga (southern Spain) (Fig. 1), between 1994 and 2010 for the study of incidence, and during 2010, for the study of prevalence. The population of this area seeks care at the Costa del Sol Hospital in Marbella, a secondary hospital, and two nearby tertiary hospitals, Hospiten Clinic in Estepona and USP Hospital in Marbella. The nearest tertiary hospital, located in Málaga city, belongs to another health district, about 54 km from Marbella hospital, and all townships of our health district are closer to Marbella than to Málaga city (Fig. 1). All ENT, dermatology and ophthalmology departments in our district are located in our hospital. Since no rheumatology departments are available in our area, the departments of internal medicine, nephrology and pneumology of Costa del Sol Hospital take care of all patients with vasculitis.

The catchment area is located between latitude 36°18'N and 36º39'N and between longitude 04°36'W and 05°22'W (Fig. 1). The population of this area has grown considerably in recent years, from 127,522 inhabitants in 1994 to 379,334 inhabitants in 2010 (according to data from the Spanish National Institute of Statistics). In 2010, people aged over 50 years accounted for 28% of the population. This is an area with a strong tourist industry and high levels of immigration of many different nationalities. In 2010, 32.5% of the registered population in the area and 25.5% of hospital admissions were foreigners.

Sources

All patients aged 14 years or older diagnosed with vasculitis in Costa del Sol Hospital were located by automated database analysis for a period of 17 years, from the hospital's opening day, 1 January 1994, until 31 December 2010. Medical records from patients with vasculitis from the two tertiary centres in the area were transferred to Costa del Sol Hospital for their analysis and inclusion if appropriate. To minimise codification errors and possible outpatient diagnoses, we tried to identify additional cases of PSV through the analysis of data from pathology and laboratory departments, looking for biopsy proven vasculitis and serological markers of vasculitis (ANCA, cryoglobulins) respectively. In addition, we also double-checked all the information about patients with PSV with the hospital staff involved in following patients with vasculitis at outpatient clinics.

Patients diagnosed with giant cell arteritis (GCA), Takayasu's arteritis (TA), PAN, granulomatosis with polyangiitis (Wegener) (GPA), MPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (EGPA), IgA vasculitis (Henoch-Schönlein) (IgAV) and cryoglobulinaemic vasculitis (CV) were included. Because patients with complex clinical presentations leading to the final diagnosis of vasculitis or those with an initial suspected vasculitis in our centre are always diagnosed during hospitalisation, all patients were located by using the following the ICD-9 diagnostic codes: 446.5 for GCA, 446.7 for TA, 446.0 for PAN and MPA, 446.4 for GPA, 447.6 for EGPA, 287.0 for IgAV and 273.2 for CV. In order to accurately identify AAV patients, we also searched for the codes for glomerulonephritis (580.4 and 583.4) and the coexistence of the terms ANCA, cytoplasmic pattern by indirect immunofluorescence (IFI) (cANCA), perinuclear pattern by IFI (pANCA), proteinase 3 (PR3) and/or myeloperoxidase (MPO). From patients' electronic medical records, epidemiological data (sex, age, race and nationality), clinical, laboratory, radiological and histological findings were recorded. We also reviewed patients' outcomes during the follow-up to confirm the initial diagnosis of vasculitis or to detect any indicator suggesting a disease other than the PSV initially diagnosed.

Inclusion criteria

Only permanent residents were included. Inclusion criteria were based on the 1990 ACR classification criteria for GCA, TA, GPA, EGPA and IgAV (3), together with all the definitions and characteristics arised from the 2012 CHCC (2). For PAN, MPA and CV, only definitions from the 2012 CHCC were used (2).

Exclusion criteria

The patients excluded from the study were those with secondary vasculitides, including cases of CV associated with viral infections, those with leukocytoclastic vasculitis (since their identification is very difficult, due to the fact that most of the patients are diagnosed without histological confirmation at Emergency department and/or outpatient clinics and do not require hospitalisation), and those with an initial diagnosis of vasculitis subsequently not confirmed, in which an alternative diagnosis was obtained.

Statistical analysis

The incidence of the different PSV was calculated as the rate (or density) of incidence, considering that the population of the study area has grown significantly in recent years. The incidence rate was calculated as the ratio of cases of vasculitis included during the study period to the sum of the population recorded for the area each year, from 1994 to 2010, and it is expressed in cases per million population per year for all vasculitides, except for GCA, for which was calculated per 100,000 population per year aged 50 years and older. The prevalence was calculated as the patients followed up for PSV in 2010 and the census population in

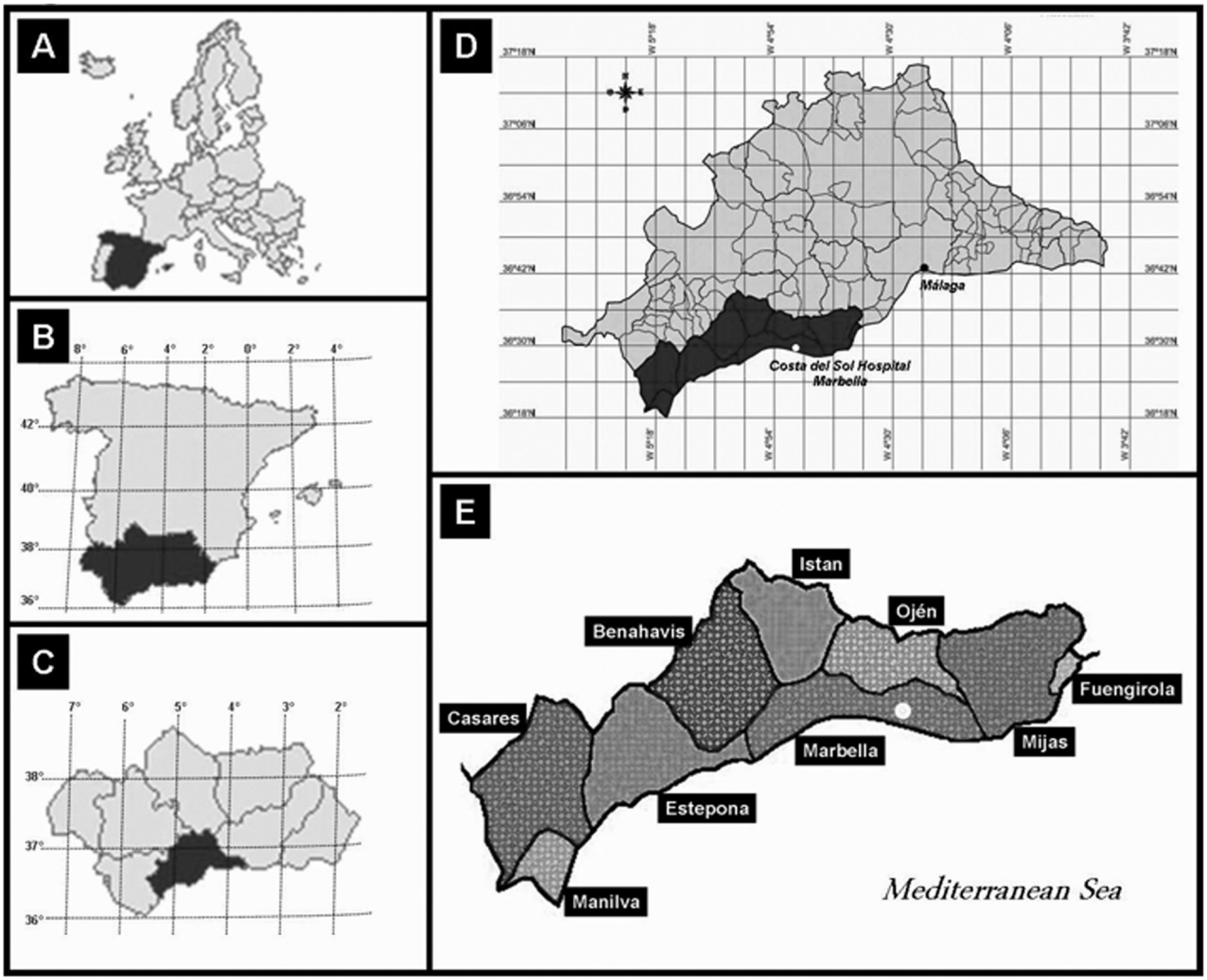

Fig. 1. Western Costa del Sol Healthcare District. Localisation in **A**. Spain; **B**. Andalucía region; **C**. Province of Málaga; **D**. West Costa del Sol Health District; and **E**. townships composing the district.

2010. It is expressed in cases per million population, except for GCA (per 100,000 population aged 50 years and older). Confidence intervals (95%CI) for the different incidence rates were estimated assuming Poisson distribution. Confidence intervals (95%CI) of the prevalence were calculated according to Wald's formula.

Statistical analysis was performed using SPSS version 15.0. For each variable considered, the mean (and range) and percentages were calculated for quantitative and qualitative variables, respectively.

Results

We analysed a total of 179 patients with known or suspected vasculitis during the study period. Of these, 74 patients definitively diagnosed with PSV were finally included. The final diagnoses encompassed GCA in 29 patients (39.1%), TA in 5 (6.7%), PAN in 3 (4%), AAV in 29 (39.1%) [including GPA 10 (13.5%), MPA 16 (21.6%) and EGPA 3 (4%)], IgAV in 7 (9.4%) and CV in 1 (1.3%) patient (Table I). Seventy-two out 74 patients were diagnosed at Costa del Sol Hospital and two (both GCA) at Hospiten Clinic of Estepona. Thirteen patients were diagnosed or followed at the department of nephrology (10 MPA, 1 GPA and 2 IgAV) and 61 patients at the department of internal medicine (four of them were initially diagnosed at the department of pneumology). No patient was transferred to a tertiary hospital either at the time of diagnosis or during the follow-up.

Of the remaining 105 patients, 20 were diagnosed with biopsy-proven leukocytoclastic vasculitis (9 cases related to viral or bacterial infections, 2 with drug induced vasculitis and 9 with limited cutaneous leukocytoclastic vasculitis; none of them met criteria for IgAV or CV), six patients were finally diagnosed with autoimmune diseases, four with Behçet's disease and four with CV associated with hepatitis C virus (HCV) infection (one of them with coinfection by HCV and HIV). Two patients had a single-organ vasculitis, namely cutaneous arteritis and primary vasculitis of the central nervous system. In the remaining 69 cases, after a comprehensive study, the diagnostic suspicion of vasculitis was not confirmed and final diagnoses included non-classifiable

Table I. Epidemiological data of the primary systemic vasculitides diagnosed in Costa del Sol of Marbella (Málaga, Spain) from 1994 to 2010.

Vasculitis type	n (%)	Age (mean; range)	Sex F/M	Foreign patients n (%)*	Annual incidence rate (95%CI)‡	Prevalence (95%CI); n in 2010#
GCA	29 (39.1)	71.5 (53-81)	19/10	7 (24.1)	2.2 (1.4-3.0)	12.2 (5.6-18.9); 13
TA	5 (6.7)	26 (17-34)	5/0	2 (40)	1.1 (0.1-2.0)	10.5 (0.2-20.8); 4
PAN	3 (4)	58 (34-83)	2/1	1 (33)	0.6 (0-1.3)	2.6 (0-7.6); 1
AAV	29 (39.1)	61.3 (36-82)	16/13	4 (13.8)	6.2 (3.9-8.4)	44.8 (23.5-66.1); 17
GPA	10 (13.5)	55.8 (36-76)	5/5	1 (10)	2.1 (0.8-3.4)	15.8 (3.1-28.4); 6
MPA	16 (21.6)	66 (46-82)	9/7	3 (18.7)	3.4 (1.7-5.1)	23.8 (8.2-39.2); 9
EGPA	3 (4)	55 (46-69)	2/1	0	0.6 (0-1.3)	5.3 (0-12.5); 2
IgAV	7 (9.4)	47.7 (15-84)	1/6	0	1.5 (0.3-2.6)	7.9 (0-16.8); 3
CV	1 (1.3)	84 (-)	0/1	0	0.2 (0-0.6)	0; 0
Overall	74	62 (15-84)	43/31	14; 19	15.8 (12.2-19,4)	100.1 (68.3-132.0); 38

F: female; M: male. *Nationality of foreign patients: GCA: North Europe (n=7); TKA: Morocco (n=1) and Ecuador (n=1); PAN: Senegal (n=1); GPA: Philippines (n=1) and MPA: Germany (n=1), Morocco (n=1) and Peru (n=1).
‡Annual incidence rate is expressed per million inhabitants, except for GCA (100,000 inhabitants >50 years/year); #Prevalence by 2010, expressed per million inhabitants, except for GCA (100,000 inhabitants >50 years).

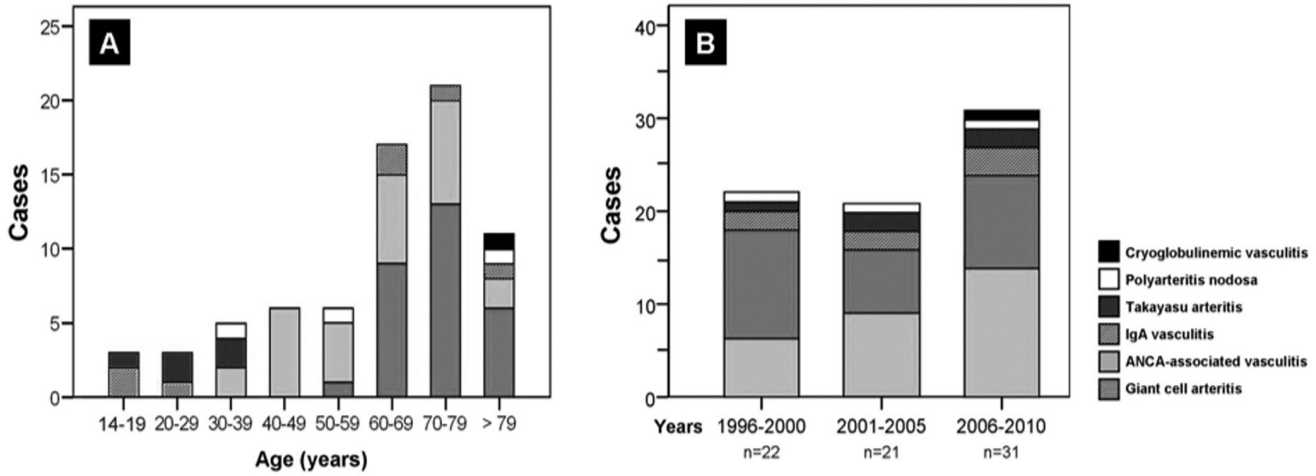

Fig. 2. A. Distribution of primary systemic vasculitides in the current study according to the age of the patients at diagnosis.
B. Distribution of primary systemic vasculitides diagnosed during the study period at 5-year intervals.

inflammatory conditions, infections and cancer. Twelve patients had been diagnosed with PSV prior to the study period, and therefore were not included in the study of incidence. Of these, two patients with GCA, diagnosed by biopsy of the temporal artery, and one with GPA, diagnosed by renal biopsy, were included only in the prevalence study.
Therefore, 74 patients were included in the incidence study, whereas only 38 patients were being followed up in the study area in 2010, and were used for prevalence calculations.

Diagnosis of the primary systemic vasculitides

The 29 patients with GCA met at least three of the ACR classification criteria for GCA. Temporal artery biopsy was performed in 19 of them, 12 (62%) of which were positive. Any patient developed manifestations suggesting a different disease during the follow-up period. The five patients diagnosed with TA met the ACR criteria, and all patients had a confirmative vascular study. Only three of the four patients initially classified as PAN (4) were classified as PAN according to the current CHCC recommendations (2). In two of them, a tissue biopsy disclosed medium vessel necrotising vasculitis, and in all three, angiography revealed visceral aneurysms.
Of the 29 cases with AAV, a renal biopsy was performed in 12 (41.3%) patients, which was diagnostic of vasculitis in all of them. In five patients without renal disease, four out eight biopsies performed in other territories showed vasculitis. Overall positivity for ANCA (either by IFI or ELISA) was 89%. As for the type of ANCA positivity, 80% of GPA patients were cANCA (88% PR3) and 10% pANCA (0 MPO); in MPA, 86% were pANCA/MPO and 14% cANCA/PR3; and in EGPA, 66% were pANCA (50% MPO) with no cases of cANCA/PR3.
All seven adult patients with IgAV were diagnosed by skin biopsy and clinical features. Two patients presented IgA deposits at immunofluorescence and a renal biopsy revealed an IgA mesangioproliferative glomerulopathy in another patient. Only one patient was diagnosed with CV (type III essential cryoglobulinaemia).

Epidemiological data

The 74 patients with PSV diagnosed over 17 years (1994–2010), among a total population of 4,682,098 persons

per year of observation, represent an annual incidence rate of 15.8 (95%CI 12.2-19.4) cases per million inhabitants. The 38 patients with vasculitis who remained in follow-up in 2010, among a population of 379,334 inhabitants, represent a prevalence of 100.1 (95% CI 68.3–132.0) cases per million inhabitants.

The population data (sex, age and nationality), the annual incidence rate and the corresponding prevalence values for all the PSV diagnosed in Costa del Sol region are listed in Table I. Sixty patients (81%) were Spaniards. Of the 14 foreign patients (19%), eight were European, three Africans, two South Americans and one Asian. All the patients were permanent residents in the study area.

The distribution of the different PSV according to the age of the patients at diagnosis is shown in Figure 2A. The youngest patients were those diagnosed with TA and IgAV, and consecutively, PAN, AAV and GCA (mean age of 26, 48, 58, 61 and 71.5 years, respectively). The distribution of PSV diagnosed during the study period is shown in Figure 2B. After remaining stable, the number of patients diagnosed with PSV increased during the later part of 2000's decade. Among them, AAV were the vasculitides with a more noticeable increase.

Table II. Annual incidence of giant cell arteritis in different regions of the world (for a population aged over 50 years).

Region	Date	Incidence*
Iceland (10)	1984-1990	27.0
Vest Adger County, Norway (12)	1992-1996#	29.1
Göteborg, Sweden (13)	1976-1995#	22.2
Olmsted County, Minnesota, USA (38)	1950-1999	18.8
Otago region, New Zealand (44)	1996-2005	12.7
Israel (41)	1980-2004	11.3
Lugo, Spain (8)	1988-1997#	11.1
Lugo, Spain (14)	1981-2005#	10.1
Loire-Atlantique, France (16)	1970-1979	9.4
Reggio Emilia, Italy (17)	1980-1988	6.9
Sabadell, Barcelona, Spain (15)	1989-2001	4.1
United Kingdom (36)	1990-2001	2.2
Vilnius, Lithuania (9)	1990-1999	2.3
Shelby County, Tennessee, USA (39)	1971-1980	
- White population		2.2
- Afroamerican population		0.4
Thrace region, northwestern Turkey (29)	2002-2008	1.13
Costa del Sol, Málaga, Spain*	1994-2010	2.2

*Present study; #Only patients with biopsy proven GCA were included.

Discussion

Our study confirms that PSV are rare diseases also in our region. Two epidemiological studies performed in northern Germany (7) and northwestern (NW) Spain (8) analysed a similar number of vasculitides as those included in the current study besides Kawasaki disease (7) and isolated leukocytoclastic vasculitis (7, 8). They found a higher annual incidence of PSV (40–54 and 115.04 cases per million population, respectively) than in our region in southern Spain (15.8 cases per million population). The high rate of patients with vasculitis found in Lugo (NW Spain) with respect to that found in Germany is due in part to the high proportion (24%) of patients with leukocytoclastic vasculitis included in the study (8).

The main studies of GCA incidence carried out to date reflect a descending gradient from north to south, affecting European and American latitudes equally (Table II). Except for the low results found in UK (36) and Lithuania (9), the incidence is higher in northern European countries (10-13) and in northern areas of North America (38) (both areas featuring people of Scandinavian ancestry), and lower in Mediterranean countries (8, 14-17), including Turkey (29) and Israel (41). An annual incidence of 12.7 found in New Zealand (southern Hemisphere) might be explained in part by the European background of the majority of patients (44). In Shelby County (Tennessee, US), another southern area located in a similar latitude than Costa del Sol (Spain), GCA incidence is similar to ours (39). This US study also reflects the rarity of this type of vasculitis among the Afro-American population (39). GCA in Japan is also rare, with a prevalence of 1.47 per 100,000 population older than 50 years in 1998, which indicates a prevalence 40 to 75 times lower than that found in North-Western countries (48).

In Spain, the annual incidence of GCA also presents the same descending gradient from north to south. Thus, the values are lower in our region than in the north of Spain, specifically in the areas of Lugo (NW Spain) (14) and Sabadell (Barcelona, NE Spain) (15), where the annual incidence were 10.1 and 4.1 cases per 100,000 inhabitants over 50 years, respectively (Table II).

The annual incidence of TA in our population (1.06 per million inhabitants) is similar to other European countries (such as the UK, Germany, Sweden and Lithuania) and lower than in USA (Table III). Although the incidence of TA in Japan is not very different from that found in Western countries, its prevalence in Japan and other Asian countries is much higher than that reported in the USA and some European countries (31, 49). All these studies have been summarised in a recent review (31). No cases of TA were found in northwestern Spain (8). In this regard, differences between these two Spanish regions might be explained by the fact that the population of the northern region, with Celtic background, was very homogeneous and still relatively isolated in the 1980–90s, whereas in our southern area, with mixed population, the presence of foreign people (40% of TA) seems to account for higher or relevant incidence/prevalence.

The well known low frequency of PAN was confirmed in our area, with similar results to those found in other parts of Europe, such as the UK, Germany, the Scandinavian countries and north-

Table III. Epidemiology of Takayasu arteritis in different regions of the world.

City/Region/Country	Population	Year	Incidence	Prevalence
Schleswig-Holstein, Germany	2,777,275	1998-2002	0.4-1.0	NS
Sweden	1,300,000	1969-1975	0.8	6.4
Norwich, England	445,000	2000-2005	0.8	4.7
Vilnius, Lithuania	468,504	1990-1999	1.3	NS
Olmsted County, USA	88461*	1971-1982	2.6	NS
Lugo, Spain (8)	250,000	1988-1997	0	NS
Japan	NS#	1982-1984	1-2	NS
Japan	NS	1994	NS	40
Kuwait	1,240,000	1989-1994	2.2	7.8
Costa del Sol, Malaga, Spain**	379,334	1994-2010	1.1	10.5

Adapted from reference (31). Annual incidence and prevalence are expressed per million inhabitants. NS: Not stated. #Carried out as part of a nationwide epidemiological study; *Population/year of observation 1,150,000, for 13 years, equivalent to a stable population of 88,461 inhabitants; **Present study.

ern Spain, and also Australia and Peru, where the annual incidence of PAN ranges between 0 and 2.3 cases per million inhabitants (7, 8, 20, 23, 26, 30, 42, 43) (Table IV). In an epidemiological study of PSV (between 1988-1998) comparing the results of Norwich (UK), Lugo (Spain) and Tromsǿ (Norway), after applying the ACR classification criteria, the annual incidence for PAN was 9.7, 6.2 and 4.4 cases per million, respectively. However, when CHCC definition for PAN was used, the annual incidence decreased to 0, 0.9 and 0.5 cases per million respectively (20). These results illustrate the difficulty of comparing clinical and epidemiological studies of patients diagnosed with PAN before its differentiation from MPA in 1994 CHCC. The prevalence of PAN varies among studies (Table IV). Although a German (19) and a Norwegian (18) study showed a similar prevalence to that found in our area, other studies have reported a significant higher prevalence (22, 25, 43), which might have been influenced by the inclusion of patients with HBV infection.

Table IV. Annual incidence and prevalence of AAV and PAN in the different epidemiological studies.

ANNUAL INCIDENCE City/Region	Date	GPA	MPA	EGPA	PAN#	Global
Tromsø, Norway (20)	1988-1998	10.5	2.7	0.5	0.5	13.7
Kristiansand, southern Norway (18)	1992-1996	6.7	6.7	2.7	-	-
Scania, southern Sweden (30)	1997-2006	9.8	10.1	0.9	0.9	21.8
Faroe Islands (37)	1992-2011	6.4	-	-	-	-
Norwich, UK (20)	1988-1998	10.6	8.4	3.1	0	18.9
Norfolk, UK (24)	1988-2010	10.8	5.7	2.9	-	19.5
Baden-Württemberg, southern Germany (23)	1998-1999	5.5	1.5	1	1	9
Schleswig-Holstein, northern Germany (23)	1998-1999	7	3	1	1.5	12.5
Schleswig-Holstein, northern Germany (7)	1998-2002	6-12	3	1	0.4-2	9.5-16
Greenland (37)	1992-2011	1	-	-	-	-
Vilnius, Lithuania (9)	1990-1999	2.1	3	1.3	-	-
Montana, USA (40)	1993-2004	8.6	2.9	-	-	11.4
Australia (different regions) (43)	1995-1999	8.8	2.3	2.3	2.3	17
	2000-2004	8.4	5	2.2	1.1	16
Miyazaki (Japan) (46)	2000-2004	0	14.8	0	-	14.8
Miyazaki (Japan) (47)	2005-2009	2.1	18.2	2.4	-	22.6
Lima, Peru (42)	1990-2004	0.5	4.0	0.1	0.5	5.1
Lugo, Spain (8)	1988-1997	4.8	4.0	1.1	1.0	-
Lugo, Spain (20)	1988-1998	4.9	11.6	0.9	0.9	18.3
Lugo, Spain (26)	1998-2001	2.9	7.9	1.3	0.9	13.0
Costa del Sol, Malaga, Spain*	1994-2010	2.1	3.4	0.6	0.6	6.7

PREVALENCE City/Region/Country	Date	Population	GPA	MPA	EGPA	PAN	Global
Kristiansand, southern Norway (18)	1996	150,426	5.3	-	1.3	3.3	-
Lund, southern Sweden (22)	2003	287,479	156	66	7	28	257
Norfolk, UK (24)	2010	340.000	148	65	46	-	255
Schleswig-Holstein, northern Germany (19)	1994	449,498	58	9	7	9	83
Baden-Württemberg, southern Germany (19)	1994	426,485	42	0	2	2	46
Seine-St. Denis, France (25)	2002	1,093,515	24	25	11	31	90
Montana, USA (40)	2004	-	9	3	-	-	12.1
Australia (different regions) (43)	1995-1999	431,199	64	17.5	12	20.5	114
	2000-2004	451,337	95	39	22	22	184
Canterbury, New Zealand (45)	1999-2003	481,000	152	58	-	-	-
Japan (nationwide survey) (46)	1998	-	2.3	13.8	1	-	17.1
Costa del Sol, Málaga, Spain*	2010	379,334	15.8	23.8	5.3	2.6	47.5

Values are expressed per million population per year. *Present study. #For annual incidence results, only studies using Chapel Hill definition criteria for PAN (1, 2) are included.

Our findings regarding AAV fit with the north-south pattern reported for Europe, with a higher number of cases of GPA in northern Europe and a higher frequency of MPA in the Mediterranean countries (21, 50). When discrepancies in this gradient are found, these may be influenced by the inclusion criteria and the source of recruitment, and in particular, in series in which renal involvement is required MPA usually predominates over GPA (50). Except for the Inuit population of Greenland (37), who has a remarkably low incidence of GPA, compared to the Costa del Sol region, the incidence and/or prevalence of GPA and MPA is higher in the northern and western European countries (7, 18-20, 22-25), NW Spain (8, 20, 26), Australia (43), New Zealand (45), Montana (United States; for GPA) (40) and Japan (for MPA) (46, 47). Other MPA studies have obtained similar or slightly lower results (7, 9, 20, 23, 25, 40) to ours (Table IV). In addition, EGPA incidence in our region is lower than in other countries (7-9, 18, 20, 23, 24, 26, 30, 43, 47) (Table IV). In Japan, almost exclusively predominates MPA, with a very low prevalence of GPA and EGPA as demonstrated by a 1998 nationwide survey in Japan showing an AAV prevalence of 17.1 per million (MPA/RLAAV 13.8, GPA 2.3 and EGPA 1.0 per million) (46). A recent study in Miyazaki (Japan) corroborated these global Japanese data and found that the average annual incidence of AAV over the 5-year period was 22.6 per million of adult population (MPA 18.2, GPA 2.1 and EGPA 2.4) (47). Of note, only two epidemiological studies including all the AAV conducted in Lima (Peru) (42) and Vilnius (Lithuania) (9) observed similar results to those obtained in our area.

IgAV is the vasculitis most common in childhood, occurring two to 33 times more frequently in children than in adults (51). A recent review including different IgAV series has found an annual incidence rate for children that ranges from 3 to 26.7 per 100,000 inhabitants (51). Epidemiological studies of IgAV in adults are scarce. Whereas a German study including patients of all ages found 3–10 cases of IgAV per million inhabitants (7), two studies with adult patients performed in the UK and NW Spain found an annual incidence of 13 and 14.3 cases per million population, respectively (28, 34). Interestingly, in the same area of NW Spain, the annual incidence rate of IgAV in children and adults has been analysed, being of 10.45 per 100,000 people aged 14 years and younger and 14.3 cases per million inhabitants >20 years, respectively (27, 28). In our area, the annual incidence of 1.85 cases per million inhabitants >14 years is notably lower than that found in UK and NW Spain.

To date, no data have been published for the prevalence or incidence of essential CV. Although most cases (about 60–90%) of CV are produced by or associated with HCV infection, of the remainder, not considered secondary to infection, about half are eventually diagnosed as essential or idiopathic CV, a third are associated with an autoimmune disease and 20% are associated with a lymphoproliferative disease (52). In large series of patients with systemic vasculitides, essential CV represented from 0 (53) to 3.4% (8) of all cases of PSV. Our finding of an annual incidence of 0.2 cases per million and prevalence of 0 cases per million highlights the rarity of essential CV.

In the Costa del Sol region, the proportion of foreign patients diagnosed with PSV is lower than that corresponding to foreigners in the general population (19% *vs*. 32.5%). Except for TA, for which the proportion of foreigners (40%) is higher than in general population, the remaining results in this regard do not allow us to draw firm conclusions about the influence of the foreign population on the epidemiology of vasculitis in our region.

The main limitations of this study, which would have underestimated the present results, include possible coding errors and selection bias, the existence of patients who might not have required admission and had been diagnosed and followed at our outpatient clinics or in other centres (such as primary care facilities), and patients who might have sought care in a tertiary hospital (further away than our hospital for all the townships of our area). To the best of our knowledge, patients with any suspected systemic vasculitis seen by family doctors in our health district are usually transferred to our hospital. Finally, although all patients with leukocytoclastic vasculitis admitted for study did not meet criteria for IgAV, the markedly lower incidence of IgAV in our population compared to other studies, still generates doubts whether mild forms of IgAV could have been missed.

Conclusions

This is the first epidemiological study of PSV conducted in southern Spain. The incidence and prevalence results obtained confirm the rarity of vasculitides in our area and that they occur less frequently than in countries in the Northern Hemisphere, and in particular, than in regions of northern Spain. GCA and AAV are the vasculitides that are most frequently PSV diagnosed in our region.

References

1. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
2. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. FRIES JF, HUNDER GG, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum* 1990; 33: 1135-6.
4. LIGHTFOOT RW, JR., MICHEL BA, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33: 1088-93.
5. WATTS RA, CARRUTHERS DM, SCOTT DG: Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum* 1995; 25: 28-34.
6. GONZALEZ-GAY MA, GARCIA-PORRUA C: Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 2001; 27: 729-49.
7. REINHOLD-KELLER E, HERLYN K, WAGNER-BASTMEYER R, GROSS WL: Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. *Arthritis Rheum* 2005; 53: 93-9.
8. GONZALEZ-GAY MA, GARCIA-PORRUA C: Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine* (Baltimore) 1999; 78: 292-308.
9. DADONIENE J, KIRDAITE G, MACKIEWICZ Z *et al*.: Incidence of primary systemic vasculitides in Vilnius: a university hospital population based study. *Ann Rheum Dis* 2005; 64: 335-6.

10. BALDURSSON O, STEINSSON K, BJORNSSON J, LIE JT: Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. *Arthritis Rheum* 1994; 37: 1007-12.
11. GONZALEZ-GAY MA, VAZQUEZ-RODRIGUEZ TR, LOPEZ-DIAZ MJ *et al*.: Epidemiology of giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum* 2009; 61: 1454-61.
12. HAUGEBERG G, PAULSEN PQ, BIE RB: Temporal arteritis in Vest Agder County in southern Norway: incidence and clinical findings. *J Rheumatol* 2000; 27: 2624-7.
13. NORDBORG C, JOHANSSON H, PETURSDOTTIR V, NORDBORG E: The epidemiology of biopsy-positive giant cell arteritis: special reference to changes in the age of the population. *Rheumatology* (Oxford) 2003; 42: 549-52.
14. GONZALEZ-GAY MA, MIRANDA-FILLOY JA, LOPEZ-DIAZ MJ *et al*.: Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine* (Baltimore) 2007; 86: 61-8.
15. BUSTAMANTE MALDONADO E, MARI ALFONSO B, MONTEAGUDO JIMENEZ M *et al*.: [Analysis of a series of 55 patients with biopsy proven giant cell temporal arteritis]. *An Med Interna* 2004; 21: 473-6.
16. BARRIER J, PION P, MASSARI R *et al*.: [Epidemiologic approach to Horton's disease in the department of Loire-Atlantique. 110 cases in 10 years (1970-1979)]. *Rev Med Interne* 1982; 3: 13-20.
17. SALVARANI C, MACCHIONI P, ZIZZI F *et al*.: Epidemiologic and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. *Arthritis Rheum* 1991; 34: 351-6.
18. HAUGEBERG G, BIE R, BENDVOLD A *et al*.: Primary vasculitis in a Norwegian community hospital: a retrospective study. *Clin Rheumatol* 1998; 17: 364-8.
19. REINHOLD-KELLER E, ZEIDLER A, GUTFLEISCH J *et al*.: Giant cell arteritis is more prevalent in urban than in rural populations: results of an epidemiological study of primary systemic vasculitides in Germany. *Rheumatology* (Oxford) 2000; 39: 1396-402.
20. WATTS RA, LANE SE, SCOTT DG *et al*.: Epidemiology of vasculitis in Europe. *Ann Rheum Dis* 2001; 60: 1156-7.
21. LANE SE, WATTS R, SCOTT DG: Epidemiology of systemic vasculitis. *Curr Rheumatol Rep* 2005; 7: 270-5.
22. MOHAMMAD AJ, JACOBSSON LT, MAHR AD *et al*.: Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. *Rheumatology* (Oxford) 2007; 46: 1329-37.
23. REINHOLD-KELLER E, HERLYN K, WAGNER-BASTMEYER R *et al*.: No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register. *Rheumatology* (Oxford) 2002; 41: 540-9.
24. WATTS RA, MOONEY J, SKINNER J *et al*.: The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. *Rheumatology* (Oxford) 2012; 51: 926-31.
25. MAHR A, GUILLEVIN L, POISSONNET M, AYME S: Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum* 2004; 51: 92-9.
26. GONZALEZ-GAY MA, GARCIA-PORRUA C, GUERRERO J *et al*.: The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. *Arthritis Rheum* 2003; 49: 388-93.
27. CALVINO MC, LLORCA J, GARCIA-PORRUA C *et al*.: Henoch-Schonlein purpura in children from northwestern Spain: a 20-year epidemiologic and clinical study. *Medicine* (Baltimore) 2001; 80: 279-90.
28. GARCÍA-PORRÚA C, GONZÁLEZ-GAY MA: Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schonlein purpura in adults. *Semin Arthritis Rheum* 1999; 28: 404-12.
29. PAMUK ON, DONMEZ S, KARAHAN B *et al*.: Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: Clinical features and epidemiological data. *Clin Exp Rheumatol* 2009; 27: 830-3.
30. MOHAMMAD AJ, JACOBSSON LT, WESTMAN KW *et al*.: Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. *Rheumatology* (Oxford) 2009; 48: 1560-5.
31. WATTS R, AL-TAIAR A, MOONEY J *et al*.: The epidemiology of Takayasu arteritis in the UK. *Rheumatology* (Oxford) 2009; 48: 1008-11.
32. WATTS RA, GONZALEZ-GAY MA, LANE SE *et al*.: Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. *Ann Rheum Dis* 2001; 60: 170-2.
33. WATTS RA, LANE SE, BENTHAM G, SCOTT DG: Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000; 43: 414-9.
34. WATTS RA, SCOTT DG: Epidemiology of the vasculitides. *Semin Respir Crit Care Med* 2004; 25: 455-64.
35. WATTS RA, SCOTT DG: Recent developments in the classification and assessment of vasculitis. *Best Pract Res Clin Rheumatol* 2009; 23: 429-43.
36. SMEETH L, COOK C, HALL AJ: Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. *Ann Rheum Dis* 2006; 65: 1093-8.
37. FAURSCHOU M, HELLEBERG M, OBEL N, BASLUND B: Incidence of granulomatosis with polyangiitis (Wegener's) in Greenland and the Faroe Islands: epidemiology of an ANCA-associated vasculitic syndrome in two ethnically distinct populations in the North Atlantic area. *Clin Exp Rheumatol* 2013; 31: S52-5.
38. SALVARANI C, CROWSON CS, O'FALLON WM *et al*.: Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. *Arthritis Rheum* 2004; 51: 264-8.
39. SMITH CA, FIDLER WJ, PINALS RS: The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. *Arthritis Rheum* 1983; 26: 1214-9.
40. ZETF A, M. S, WEISS N, EMERY H: Case control study of ANCA-associated vasculitis in Western Montana. *Arthritis Rheum* 2005; 52: S648 (abstract).
41. BAS-LANDO M, BREUER GS, BERKUN Y *et al*.: The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. *Clin Exp Rheumatol* 2007; 25: S15-7.
42. SÁNCHEZ TORRES A, ACEVEDO VÁSQUEZ E, SÁNCHEZ SCHWARTZ C *et al*.: [Epidemiology of primary systemic vasculitides in a Latinoamerican population]. *Reumatología* 2005; 21: 145-50.
43. ORMEROD AS, COOK MC: Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. *Intern Med J* 2008; 38: 816-23.
44. ABDUL-RAHMAN AM, MOLTENO AC, BEVIN TH: The epidemiology of giant cell arteritis in Otago, New Zealand: a 9-year analysis. *N Z Med J* 2011; 124: 44-52.
45. GIBSON A, STAMP LK, CHAPMAN PT, O'DONNELL JL: The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. *Rheumatology* (Oxford) 2006; 45: 624-8.
46. FUJIMOTO S, UEZONO S, HISANAGA S *et al*.: Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. *Clin J Am Soc Nephrol* 2006; 1: 1016-22.
47. FUJIMOTO S, WATTS RA, KOBAYASHI S *et al*.: Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology* (Oxford) 2011; 50: 1916-20.
48. KOBAYASHI S, YANO T, MATSUMOTO Y *et al*.: Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. *Arthritis Rheum* 2003; 49: 594-8.
49. NASU T: Takayasu's truncoarteritis in Japan. A statistical observation of 76 autopsy cases. *Pathol Microbiol* (Basel) 1975; 43: 140-6.
50. CORRAL-GUDINO L, BORAO-CENGOTITA-BENGOA M, LERMA-MARQUEZ JL, DEL PINO-MONTES J: Differences in the incidence of microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's). Is there a latitudinal gradient? *J Rheumatol* 2011; 38: 2494-6.
51. PIRAM M, MAHR A: Epidemiology of immunoglobulin A vasculitis (Henoch-Schonlein): current state of knowledge. *Curr Opin Rheumatol* 2013; 25: 171-8.
52. TERRIER B, KRASTINOVA E, MARIE I *et al*.: Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood* 2012; 119: 5996-6004.
53. SORENSEN SF, SLOT O, TVEDE N, PETERSEN J: A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. *Ann Rheum Dis* 2000; 59: 478-82.