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ANCA-Negative Pauci-Immune Glomerulonephritis: A Review

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Abstract
Background: Pauci-immune glomerulonephritis (PIGN) is typically secondary to antineutrophil cytoplasmic antibodies (ANCA) small-vessel vasculitis. However, some cases lack detectable circulating ANCA and are called ANCA-negative PIGN (seronegative PIGN). The reported incidence of this varies greatly. Its relationship to ANCA-associated vasculitis (AAV) is unclear. ***Summary:*** This review explores the pathophysiology of seronegative PIGN and summarizes findings from 12 studies focusing on this disease. The role of neutrophils appears to be central, with activation through cellular and humoral mechanisms. Most studies have noted less extrarenal involvement and more chronic changes in the kidney biopsy in seronegative PIGN compared to ANCA-positive cases. Studies have mostly reported using corticosteroids with cyclophosphamide for induction therapy and azathioprine for maintenance. The renal survival was noted to be lower compared to ANCA-positive PIGN. ***Key Messages:*** Whether ANCA-negative PIGN represents a distinct disease or is part of the AAV spectrum remains unclear. Prospective large-scale studies are needed to understand this disease for optimal diagnosis and management.

Introduction

Pauci-immune glomerulonephritis (PIGN) is a common cause of rapidly progressive glomerulonephritis [1, 2]. It is characterized by necrotizing and crescentic glomerulonephritis, with limited immunoglobulin and complement staining in immunofluorescence microscopy. Most cases of PIGN are caused by small-vessel vasculitis, mostly granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and renal-limited vasculitis.

PIGN is typically associated with antineutrophil cytoplasmic antibodies (ANCA). However, some cases lack detectable circulating ANCA [3]. The reported magnitude of this phenomenon varies, with some studies indicating an incidence of 2%–6% [4, 5], while others, particularly from Asia, report higher occurrence rates of up to 33%–49.5% [6–13] (Table 1).

This review aims to illuminate primary ANCA-negative PIGN (seronegative PIGN). It will explore its potential underlying pathophysiological mechanisms and discuss secondary causes. We summarize the clinical features of seronegative PIGN based on 12 case series [4, 6–16]. The pathological characteristics of this entity will also be described, along with an overview of the therapeutic options.

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Pathogenesis of Primary ANCA-Negative PIGN

It is well known by now the pathogenic role that antibodies against myeloperoxidase (MPO) and proteinase 3 (PR3) have in AAV, as supported by both in vitro and animal studies [4, 17]. These are generated due to a multifactorial loss of immune tolerance to these two enzymes of the polymorphonuclear granules [18, 19]. These antibodies bind to MPO and PR3, present on the neutrophil membrane due to prior priming of these cells, either by pro-inflammatory cytokines or complement pathway products, activating them and stimulating their degranulation, thus releasing free oxygen radicals and lytic enzymes, and forming neutrophil extracellular traps, with the consequent vascular damage and vasculitis [20].

The pathogenesis of seronegative PIGN is not fully understood, and it is uncertain whether it is a component of the AAV spectrum or a distinct disease entity [5]. Interestingly, based on a recent study by Moura et al. [21], which found no cases of PIGN among 110 patients diagnosed with GPA who had undetectable ANCA levels, one could speculate that the latter might be true.

There is always the possibility that ANCA negativity corresponds to a false-negative result. This could be due to a low sensitivity of the test, which is now less likely because of the improved performance of modern assays. As shown in the European Vasculitis Society (EUVAS) study, in general, antigen-specific immunoassays showed high and similar diagnostic performances, despite different assay generations and formats, and most of them outperformed indirect immunofluorescence for ANCA determination [22]. Also, theoretically, antibody levels can fluctuate and, at a given time, can fall below the detection limit of the assay [23]; however, studies that repeated serology testing during follow-up did not observe seroconversion [4, 9, 14]. In addition, false-negative ANCA test results may be attributed to antibody reactivity to inadequately evaluate epitopes in ANCA assays [22]; Roth et al. [24] found that some PIGN patients have circulating ANCA against a linear epitope of MPO hidden by a peptide fragment of ceruloplasmin in serum. Finally, while most commercial ANCA antigen-specific immunoassays are designed to detect IgG ANCA, other Ig subclasses, like IgA ANCA, have also been identified and can stimulate neutrophils [25].

Neutrophil Activation

Neutrophils play a central role in inducing vascular injury in AAV and are activated by ANCA. Interestingly, in seronegative PIGN patients, serum levels of neutrophil gelatinase-associated lipocalin and lactoferrin are higher compared to ANCA-positive patients [26]. Additionally, renal neutrophil infiltration is more intense in ANCA-negative PIGN patients [27]. This suggests that neutrophils are essential for the development of PIGN; however, the exact mechanisms behind this remain unclear. Neutrophils may be activated by non-ANCA antibodies and/or by immune cell-mediated mechanisms [3]. Regarding the latter, high levels of IL-6 has been described in this disease and could play an essential role in indirectly activating neutrophils [28]; additionally, IL-8 and IL-17 could potentially contribute to neutrophil recruitment and activation, although their specific roles in this disease have not been studied [3]. Another possible explanation for the neutrophil influx and activation in the glomeruli is through C5a, as seronegative PIGN patients exhibit a more intense activation of the alternative complement pathway [5].

Other Antibodies

Patients with seronegative PIGN may have other circulating non-MPO-nor-PR3 antibodies. Similar outcomes obtained with rituximab compared to other induction options reported in one series [4] support this; however, rituximab may also exert effects beyond those regarding autoantibody generation, including dampening an autoimmune CD8+ T-cell response by B-cell depletion [29].

Anti-hLAMP2 Antibodies

Lysosome-associated membrane protein-2 (LAMP-2) is a glycosylated transmembrane protein found in lysosomal and plasma membranes. Among other functions, it regulates autophagic processes [30]. It varies in carbohydrate chain complexity and molecular mass between neutrophils and glomerular endothelial cells [31].

ANCA-positive patients have a high prevalence of antibodies against hLAMP-2 (80–90%), which react with endothelial and neutrophil hLAMP-2 [31]. These antibodies disappear upon immunosuppressive treatment and resurface upon clinical relapse [31]. In seronegative PIGN patients, anti-hLAMP-2 antibodies were found in 73% of cases, but they did not bind to neutrophil hLAMP-2, suggesting the possibility that autoantibody binding to hLAMP-2 in the glomerulus is sufficient to cause injury [32].

The critical question regarding these autoantibodies is whether they are pathogenic or simply an epiphenomenon. In rats, it was shown that injection of IgG to recombinant LAMP-2 caused the development of glomerulonephritis [33]. Also, based on molecular mimicry

Table 1. Studies about PIGN that included patients with ANCA negativity

Study	Country and design	Study years; follow-up	Number of patients and ANCA status	ANCA testing; definition of ANCA negativity
Hedger et al. [6] (2000)	UK, population-based, R	1986–1996; 20 months	ANCA (+) 93 (73%), ANCA (–) 35 (27%)	IIF 100%, ELISA 20%; negative test
Eisenberger et al. [14] (2005)	France, multicenter, R	1990–2001; 162 months	ANCA (–) 20	IIF 100%, ELISA 55%; negative test
Hung et al. [7] (2006)	Taiwan, single center, R	1998–2004; 18.6 months	ANCA (+) 25 (62%), ANCA (–) 15 (38%)	ELISA 100%; negative test
Chen et al. [8] (2007)	China, single center, R	1997–2006; N/D	ANCA (+) 57 (67%), ANCA (–) 28 (33%)	IIF and ELISA 100%; negative test
Villacorta et al. [9] (2016)	Spain, two centers, R	1997–2014; 24.1 months in ANCA (–), 42.8 months in ANCA (+)	ANCA (+) 85 (74.6%), ANCA (–) 29 (25.4%)	IIF and ELISA 100%; negative test
Shah et al. [10] (2016)	USA, single center, R	1995–2009; 45.7 months	ANCA (+) 57 (77%), ANCA (–) 17 (23%)	IIF and ELISA 100%; negative test
Lee et al. [15] (2016)	South Korea, single center, R	2003–2013; 933.5 days	ANCA (+) 43 (87.5%), ANCA (–) 6 (12.5%)	100% IIF, 66.7% ELISA; negative test
Córdova-Sánchez et al. [16] (2016)	Mexico, single center, R	2004–2013; 40.5 months	ANCA (+) 56 (90.3%), ANCA (–) 6 (9.7%)	IIF and ELISA 100%; negative test
Sharma et al. [11] (2016)	India, single center, R	2006–2012; 6 months	ANCA (+) 51 (60.7%), ANCA (–) 33 (39.3%)	IIF and ELISA 100%; negative test
Ronsin et al. [4] (2022)	France, multicenter, R	2006–2018; 28 months	ANCA (–) 74 *(primary = 57; infection related = 9; malignancy related = 6; drug related = 2)*	IIF and ELISA 76%, only IF 12%, only immunodot 12%; negative test
Floyd et al. [12] (2023)	UK, single center, R	2006–2016; until 2021	ANCA (+) 114 (78%), ANCA (–) 32 (22%)	100% IIF, EliA only if IIF positive; negative test
Elahi et al. [13] (2024)	Pakistan, single center, R	1998–2008; >12 months	ANCA (+) 68 (50.7%), ANCA (–) 66 (49.2%)	IIF and ELISA 100%; negative test

R, retrospective; N/D, not described; IIF, indirect immunofluorescence.

between FimH, a bacterial adhesin, and LAMP-2, rats immunized with recombinant FimH developed antibodies to FimH that reacted with LAMP-2; the immunized animals developed PIGN [33]. Incubation of human neutrophils with a monoclonal antibody to hLAMP-2 induced their degranulation; moreover, incubation of the same monoclonal antibodies with purified human dermal microvascular endothelial cells induced apoptosis of these cells [33].

Anti-Endothelial Cell Antibodies

Anti-endothelial cell antibodies (AECAs) target various endothelial antigens and have been found in autoimmune diseases with vascular inflammation, such as AAV [34]. They may contribute to vascular damage, but their pathogenic role is unclear [3, 34, 35].

Cong et al. [36] investigated the prevalence and clinical significance of AECA in seronegative PIGN patients. They found that AECA were present in 10 out of 19 ANCA-negative patients and targeted various endothelial antigens. Specific AECA was associated with distinct clinical features, such as skin rash, thrombocytosis, and higher disease activity scores. Notably, the prevalence of AECA was higher in ANCA-positive cases (23/26) and absent in healthy controls. These findings suggest that AECA may play a role in the disease process and contribute to the differences in clinical presentation between ANCA-negative and ANCA-positive vasculitis. Potential mechanisms of vascular damage by AECA include endothelial cytotoxicity and activation; activating endothelial cells can alter the expression of adhesion

molecules and cytokine secretion, consequently promoting neutrophil adhesion, activation, and subsequent damage [36–39].

Anti-Moesin Antibodies

Moesin, a heparin-binding protein linking actin filaments to the plasma membrane, contributes, among other functions, to cell adhesion in various cell types, including neutrophils [40, 41]. Anti-moesin autoantibodies, found in some anti-MPO vasculitis patients, are associated with higher inflammatory cytokines and creatinine levels [42]. These antibodies bind to neutrophils and monocytes, inducing the release of inflammatory mediators. They could play a role in vasculitis development and exacerbation [42, 43]. Evidence regarding its presence and potential role in seronegative PIGN patients is lacking.

Anti-Plasminogen Antibodies

Antibodies against plasminogen have been identified in AAV, with a frequency approaching 25% [44]. Their presence has been associated with worse kidney function and a higher occurrence of fibrinoid necrosis and cellular crescents in kidney biopsy [44]. However, their presence in seronegative PIGN has not yet been investigated.

Minor ANCA

Minor, or unconventional, ANCA correspond to antibodies against other granule contents, such as elastase, lactoferrin, bactericidal/permeability-increasing (BPI) protein, and cathepsin G. There is little evidence of the association of minor ANCA with PIGN. Regarding the case series included in this review, only two studies tested for minor ANCA [4, 6]. However, testing was only performed in about a quarter of the patients in each study, and it is unclear if the positivity was isolated or associated with anti-MPO or anti-PR3 antibodies. Therefore, no conclusions can be drawn. Seidowsky et al. [45] reported 3 cases of MPO and PR3 antibody-negative PIGN with positivity to anti-elastase antibodies. Zhao et al. [46] described patients with GPA, MPA, or organ-limited vasculitis (including several with kidney compromise) who tested negative for both PR3 and MPO-ANCAs but positive for anti-BPI antibodies; however, another study concluded that BPI-ANCA was not correlated with PIGN [47]. In conclusion, there is weak evidence that minor ANCA positivity could have a pathogenic role in PIGN.

Complement System

Complement activation, mainly the alternate pathway (AP), is crucial in ANCA vasculitis [48]. Neutrophil activation releases factors that activate the AP, and C5a promotes neutrophil priming and recruitment, forming a positive feedback loop [49, 50]. Also, C3 degradation products such as iC3b enhance neutrophil adhesion to the endothelium [51].

It has been demonstrated that seronegative PIGN patients exhibit more intense AP activation than ANCA-positive patients [5]. The heightened degree of neutrophil activation and degranulation described in seronegative PIGN may lead to more pronounced local AP activation; another possible explanation is that this entity could be caused or exacerbated by a genetic or acquired defect in the AP [5].

Secondary Causes of ANCA-Negative PIGN

In some cases, seronegative PIGN has been linked to infections, malignancies, and drug use [4]. Previously scarcely documented in the literature, Ronsin et al. [4] reported that 23% of seronegative PIGN cases were associated with infection (12%), malignancy (8%), or drugs (2%).

Regarding infection-associated PIGN, Ronsin et al. [4] identified *Staphylococcus aureus* as the most common microorganism (4 out of 9 cases), with osteitis as the predominant infection source; other identified agents were *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Streptococcus parasanguinis*. The median interval between infection and the onset of initial signs of kidney vasculitis was 2 days. One-third of the cases exhibited extrarenal manifestations, predominantly purpura (in *S. aureus*-associated disease), while only one individual displayed low C3 levels (endocarditis due to *S. parasanguinis*) [4]. Other microorganisms that have been associated to this disease include *Candida* species, *Mycobacterium tuberculosis*, and the COVID-19 vaccine [52–54].

Associated reported malignancies include lung cancer, digestive tract cancers, lymphoproliferative diseases, and neuroendocrine endometrial tumors [4, 55]. Some drugs documented are immune checkpoint inhibitors, bevacizumab and hormone therapy for in vitro fertilization [4, 56, 57]. PIGN has also been reported in the context of mixed connective tissue disease and Fabry disease [58, 59].

Recognizing these diverse possible triggers for seronegative PIGN is crucial for clinical management. Initial evaluations should prioritize identifying infection or malignancy-related causes. Prematurely starting immunosuppressive drugs without addressing these conditions can be detrimental. This is particularly important in patients with pulmonary neoplastic nodules, as misattributing them to vasculitis can result in delayed cancer treatment [4].

Table 2. Demographic characteristics of patients with primary ANCA-negative PIGN according to ANCA status

Study	ANCA status	Age, years	Sex (% female)
Hedger et al. [6] (2000)	Positive	61	39
	Negative	61	51
Eisenberger et al. [14] (2005)	Negative	65	25
Hung et al. [7] (2006)	Positive	**59[a]**	44
	Negative	**45[a]**	46
Chen et al. [8] (2007)	Positive	**57[a]**	47
	Negative	**39[a]**	42
Villacorta et al. [9] (2016)	Positive	**62[a]**	44
	Negative	**55[a]**	31
Shah et al. [10] (2016)	Positive	60	47
	Negative	60	47
Lee et al. [15] (2016)	Positive	71	**52[a]**
	Negative	69	**0[a]**
Córdova-Sánchez et al. [16] (2016)	Positive	PR3 50, MPO 47	PR3 49, **MPO 81[a]**
	Negative	49	67
Sharma et al. [11] (2016)	Positive	47	57
	Negative	35	46
Ronsin et al. [4] (2022)	Negative	70	40
Floyd et al. [12] (2023)	Positive	**66[a]**	48
	Negative	**51[a]**	33
Elahi et al. [13] (2024)	Positive	35	46
	Negative	34	56

To simplify the data in the tables, only the average or median value is shown, without including standard deviations. [a]Reported as a statistically significant difference (also in bold).

Clinical Characteristics of Primary ANCA-Negative PIGN

Twelve retrospective studies [4, 6–16] examined a small number of patients from diverse ethnic backgrounds (Tables 1–5): 10 compared seronegative PIGN to ANCA-positive controls, while 2 focused solely on ANCA-negative cases. Discrepancies in definitions and ANCA testing methods limit direct comparison of results.

Regarding demographic characteristics, in all 12 studies, patients with seronegative PIGN were similar in age or younger than those with ANCA-positive disease (Table 2). This age difference was reported to be significant in four studies from both European and Asian ethnic backgrounds [7–9, 12]. There was no clear preponderance of any gender bias.

Kidney involvement at presentation is shown in Table 3. Seronegative PIGN patients tend to have higher proteinuria [8, 9, 13]. Similarly, one study found a higher prevalence of nephrotic syndrome compared to the ANCA-positive group [8], a finding that was also observed in the studies by Eisenberg et al. [14] and Ronsin et al. [4] when comparing these results with the existing literature [16]. No clear difference was reported in the percentage of patients requiring renal replacement therapy at presentation. However, the study by Shah et al. [10] reported worse renal function at diagnosis in patients with seronegative PIGN, whereas this difference was not significant in the other studies.

Regarding extrarenal organ involvement, the available evidence suggests a higher incidence of renal-limited disease in seronegative PIGN [7, 12], supported by a meta-analysis conducted by Floyd et al. [12]. Some, but not all studies, have reported fewer constitutional manifestations [8, 12], decreased muscle and joint symptoms [8, 11, 13], reduced skin involvement [9], less lung compromise [8, 13], decreased superior respiratory tract complications [6, 8, 10–13, 16], less ocular disease [8], and diminished neurological involvement [11] (Table 4).

Table 3. Kidney involvement at presentation in patients with primary ANCA-negative PIGN according to ANCA status

Study	ANCA status	sCr or eGFR	RRT needed, %	Proteinuria, g/day, or dipstick intensity, %	Nephrotic syndrome, %	Hematuria, %
Hedger et al. [6] (2000)	Positive	8.8 mg/dL	60	N/D	N/D	N/D
	Negative	9.7 mg/dL	56	N/D	N/D	N/D
Eisenberger et al. [14] (2005)	Negative	3.0 mg/dL	20	2.7	20	100
Hung et al. [7] (2006)	Positive	5.7 mg/dL	36	2.9	N/D	N/D
	Negative	5.5 mg/dL	27	3.1	N/D	N/D
Chen et al. [8] (2007)	Positive	6.5 mg/dL	N/D	**2.2[a]**	**8.8[a]**	N/D
	Negative	7.1 mg/dL	53.6	**5.5[a]**	**46.4[a]**	100
Villacorta et al. [9] (2016)	Positive	3.4 mg/dL	42.3	**1[a]**	5.8	100
	Negative	2.9 mg/dL	34.4	**3.1[a]**	3.4	100
Shah et al. [10] (2016)	Positive	**31.9 mL/min/ 1.73 m^2[a]**	26	N/D	N/D	92
	Negative	**16.6 mL/min/ 1.73 m^2[a]**	47	N/D	N/D	88
Lee et al. [15] (2016)	Positive	1.9 mg/dL	N/D	N/D	N/D	N/D
	Negative	4.3 mg/dL	N/D	N/D	N/D	N/D
Córdova-Sánchez et al. [16] (2016)	Positive	PR3 2.4 mg/dL MPO 2.5 mg/dL	PR3 40 MPO 19	PR3 2.3 MPO 2.7	PR3 2.9 MPO 4.8	N/D
	Negative	3.1 mg/dL	33.3	4.3	0	N/D
Sharma et al. [11] (2016)	Positive	5.6 mg/dL	45.1	1.6	N/D	76.5
	Negative	7.6 mg/dL	57.6	1.9	N/D	81.8
Ronsin et al. [4] (2022)	Negative	4.5 mg/dL	21	2.5	28	91
Floyd et al. [12] (2023)	Positive	18 mL/min/ 1.73 m^2	11	N/D	N/D	N/D
	Negative	14 mL/min/ 1.73 m^2	28	N/D	N/D	N/D
Elahi et al. [13] (2024)	Positive	9.8 mg/dL	72.1	**T 5.8, 1+ 11.7, 2+ 27.9, 3+ 46.2, 4+ 11.7[a]**	N/D	100
	Negative	8.4 mg/dL	65.2	**T 0, 1+ 6.1, 2+ 19.7, 3+ 47, 4+ 27.3[a]**	N/D	100

To simplify the data in the tables, only the average or median value is shown, without including standard deviations. N/D, not described; T, trace. [a]Reported as a statistically significant difference (also in bold).

The meta-analysis indicated a reduced presence of ear-nose-throat, ocular, and respiratory tract manifestations in this group of patients [12].

Pathological Characteristics of Primary ANCA-Negative PIGN

In ANCA-positive PIGN, the characteristic lesions, such as crescents and fibrinoid necrosis, typically occur at different stages in the same specimen. Intense endocapillary hypercellularity is uncommon, but some may be present due to leukocyte infiltration [62]. The immunofluorescence criteria vary among pathologists; a staining intensity of up to 2+ or less for immunoglobulin and complement components has been used to define an immunofluorescence pattern as pauci-immune. Electron microscopy typically reveals no or rare glomerular immune complex-type electron-dense deposits [62, 63]. In general, seronegative PIGN has similar histological findings as ANCA-positive PIGN [14, 62]. The pathological characteristics of the 12 studies are summarized in Table 5; we also included two additional studies that focused on pathological characteristics of PIGN [61, 60].

Table 4. Extrarenal involvement in patients with primary ANCA-negative PIGN according to ANCA status

Characteristics	ANCA	BVAS	General symptoms, %	Extrarenal, %	Skin, %	Lung, %	ENT, %	Ocular, %	NS, %
Hedger et al. [6] (2000)	Positive	N/D	N/D, joint 45, muscle 36	100	21	69	**60[a]**	N/D	PNS 13
	Negative	N/D	N/D, joint 41, muscle 22	100	28	47	**19[a]**	N/D	PNS 19
Eisenberger et al. [14] (2005)	Negative	18.5	85, joint/muscle 45	95	50	15	20	0	PNS 15
Hung et al. [7] (2006)	Positive	N/D	N/D	**72[a]**	N/D	72	N/D	N/D	N/D
	Negative	N/D	N/D	**27[a]**	N/D	27	N/D	N/D	N/D
Chen et al. [8] (2007)	Positive	**20.1[a]**	**Fever 66.7[a]**, fatigue 52.6, **weight loss 35.1[a], myalgia 26.3[a], arthralgia 40.4[a]**	N/D	15.8	**36.8[a]**	**Otic 31.6[a], nasal 17.5[a]**	**24.6[a]**	N/D
	Negative	**13.9[a]**	**Fever 21.4[a]**, fatigue 28.6, **weight loss 7.1[a], myalgia 7.1[a], arthralgia 7.1[a]**	N/D	17.9	**10.7[a]**	**0[a]**	**3.6[a]**	N/D
Villacorta et al. [9] (2016)	Positive	15	28.2, joint 21.1	N/D	**15.2[a]**	24.7	8.2	4.7	PNS 2.3
	Negative	15	20.6, joint 17.2	N/D	**34.4[a]**	17.2	0	0	PNS 13.7
Shah et al. [10] (2016)	Positive	8.3	N/D, joint 38.6	N/D	N/D	Nodules 26.3, infiltrates 42.1	**39[a]**	14	N/D
	Negative	7.8	N/D, joint 35.2	N/D	N/D	Nodules 23.5, infiltrates 41.2	**12[a]**	0	N/D
Córdova-Sánchez et al. [16] (2016)	Positive	PR3 20, MPO 18	PR3 77.1, MPO 61.9	N/D	PR3 17.2, MPO 0	PR3 34.3, MPO 14.3	**PR3 51.4[a]**, MPO 19	PR3 37.1, MPO 0	PR3 22.9, MPO 19
	Negative	18	33.3	N/D	33.3	0	33.3	0	0
Sharma et al. [11] (2016)	Positive	**19.9[a]**	76.5, **joint 39.2[a]**	N/D	19.6	70.6	**25.5[a]**	11.8	**17.6[a]**
	Negative	**15.4[a]**	78.8, **joint 15.2[a]**	N/D	27.3	60.6	**6.1[a]**	3	**0[a]**
Ronsin et al. [4] (2022)	Negative	N/D	51, joint 12, muscle 5	58	32	19	21	N/D	N/D
Floyd et al. [12] (2023)	Positive	N/D	**28[a]**	**61[a]**	14	25	**24[a]**	5	CNS 12
	Negative	N/D	**0[a]**	**38[a]**	25	13	**0[a]**	0	CNS 3
Elahi et al. [13] (2024)	Positive	N/D	44.1, **rheumatological 22[a]**	N/D	13.2	**44.1[a]**	**10.3[a]**	4.4	5.8
	Negative	N/D	33.3, **rheumatological 7.6[a]**	N/D	9.1	**6.1[a]**	**0[a]**	0	1.5

To simplify the data in the tables, only the average or median value is shown, without including standard deviations. The study of Lee et al. [15] was not incorporated into the table because it did not report data on the subject. N/D, not described; ENT, ear, nose, and throat; NS, nervous system; PNS, peripheral NS; CNS, central NS. [a]Reported as a statistically significant difference (also in bold).

Table 5. Pathological kidney characteristics of ANCA-negative PIGN patients compared to those with ANCA positivity (only the reported significant differences are mentioned)

Hedger 2000 [6]	Comparable number of glomeruli with crescents
Eisenberger et al. [14] (2005)	Higher frequency of glomerular sclerosis and diffuse interstitial fibrosis compared to PR3-ANCA (data on ANCA-positive patients from Hauer et al. [60])
Hung et al. [7] (2006)	More chronic glomerular lesions and less acute glomerular lesions. More glomeruli with crescents
Chen et al. [8] (2007)	Fewer normal glomeruli. More prevalent and severe interstitial fibrosis
Villacorta et al. [9] (2016)	Crescentic class most frequent in both groups (Berden classification). More cases with mesangial proliferation. Tubulitis less frequent
Shah et al. [10] (2016)	Higher degree of interstitial fibrosis
Lee et al. [15] (2016)	Comparable
Córdova-Sánchez et al. [16] (2016)	Comparable frequency of Berden classes
Sharma et al. [11] (2016)	Crescentic class most frequent in both groups (Berden classification), although more frequent in ANCA-negative; more cellular crescents in ANCA-negative. Higher degree of IFTA. Less interstitial edema
Ronsin et al. [4] (2022)	No comparison group. Focal class most frequent (Berden classification)
Floyd et al. [12] (2023)	Fewer normal glomeruli. Focal class most frequent in both groups (Berden classification)
Elahi et al. [13] (2024)	Lower frequency of glomerulosclerosis. Crescentic class most frequent in both groups; more patients with focal class and fewer patients with sclerotic class (Berden classification). More cases with mesangial proliferation
Hauer et al. [60] (2002)	Higher frequency of glomerular sclerosis, diffuse interstitial fibrosis, diffuse tubular atrophy, and tubular necrosis compared to PR3-ANCA
Iwakiri et al. [61] (2013)	Comparable frequency of Berden classes

The most consistent finding is a higher frequency of chronic tubulointerstitial damage in ANCA-negative patients [8, 10, 11, 14, 60]. Regarding Berden classification, discordant findings were reported across the different studies; the meta-analysis by Floyd et al. [12] found no significant differences in Berden categories between ANCA-negative and ANCA-positive patients.

Regarding the high frequency of nephrotic syndrome observed in seronegative PIGN, Ronsin et al. [4] did not report any association with any pathological finding. However, Villacorta et al. [9] propose that this could be explained by the finding of greater mesangial hypercellularity and a tendency toward greater endocapillary hypercellularity compared to ANCA-positive patients.

Prognosis of Primary ANCA-Negative PIGN

Some studies [7, 8, 11, 12, 15], but not all [9, 10, 16], reported a higher risk of end-stage kidney disease in patients with seronegative PIGN compared to ANCA-positive patients. The meta-analysis by Floyd et al. [12] also supports a lower kidney survival in ANCA-negative patients. Possible explanations for this could be that it corresponds to a different, and maybe more aggressive, disease than ANCA-positive PIGN and/or the existence of more chronic kidney damage at diagnosis; we speculate that the latter may be due to a delay in diagnosis associated with negative serology and fewer constitutional and extrarenal symptoms. The study by Elahi et al. [13], conducted after the mentioned meta-analysis, is the only one to report better renal survival in ANCA-negative patients; this may be due to the lower chronicity and extent of histological damage reported, possibly related to prompt diagnosis in this cohort.

Several studies [6, 8–11, 15] reported no difference in mortality risk based on ANCA status, which is also shown in the meta-analysis of Floyd et al. [12]. Higher mortality in ANCA-negative patients was reported in two studies [12, 16]. The statistical analysis conducted in the study by Floyd et al. [12] suggests that this may be secondary to the higher incidence of end-stage kidney disease. Lower mortality in ANCA-negative patients was found in the

study by Elahi et al. [13], probably related to the better renal survival reported in this cohort.

Only two studies report relapse risk according to ANCA status. Shah et al. [10] reported no differences in this regard, while Floyd et al. [12] reported a lower risk of relapse in seronegative PIGN patients. Among seronegative PIGN patients, Ronsin et al. [4] found that those classified as GPA had a higher risk of relapse than patients with MPA and renal-limited vasculitis. Further data could help define the need and duration for maintenance immunosuppression.

Regarding outcome predictors, various studies [9–11, 14] reported an association between poorer renal function at diagnosis and worse renal outcomes. Additionally, certain histological findings, such as the degree of tubulointerstitial fibrosis [4, 10], the percentage of affected glomeruli [10], and the sclerotic and mixed classes of Berden [4], were associated with progression to kidney failure. Two studies did not observe an association between histological findings and renal outcomes [11, 14]. On the other hand, some studies suggest that patient survival was associated with age [6, 14] and the need for renal replacement therapy at diagnosis [6].

Treatment of Primary ANCA-Negative PIGN

There are no controlled, prospective studies on treating seronegative PIGN, making it difficult to establish treatment recommendations. As a result, clinicians are often forced to extrapolate approaches used in ANCA-positive cases.

Various treatments have been used based on available data. Among seronegative PIGN patients who were treated, for induction, most (89–100%) received steroids [4, 6, 8–16], often combined with cyclophosphamide (33–100%) [4, 6, 8–16], rituximab (0–17%) [4, 10, 16, 64], and, less frequently, mycophenolate (0–7%) [4, 10] or azathioprine (0–6%) [6, 10]. Plasmapheresis (0–9%) [11, 12, 14] and, in rare cases, intravenous immunoglobulin [6] were also utilized. Ronsin et al. [4] reported no differences in outcomes between different types of induction treatments. Remission maintenance typically involved steroids alone (19–50%) [4, 12, 14] or schemes based on azathioprine (10–63.6%) [4, 6, 12–14], mycophenolate (24%) [4], or rituximab (12%) [4].

Conclusions

Seronegative PIGN represents 2–49.5% of PIGN cases. Its relationship to AAV remains unclear. Retrospective studies on seronegative PIGN have noted less extrarenal involvement and more chronic changes in the kidney biopsy. Most patients are treated with traditional immunosuppressive agents such as corticosteroids with cyclophosphamide or, less frequently, rituximab. In general, seronegative PIGN has worse renal survival compared to ANCA-positive PIGN. Prospective large-scale studies are needed to better understand these diseases for optimal diagnosis and management.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.K. and C.J. were involved in conceptualization. A.K. provided the initial literature review and C.J. and I.H. added more studies to the paper. C.J. and I.H. wrote the first, second, and third draft of the manuscript. A.K. edited the manuscript and is the corresponding author.

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