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## **Vasculitides and glomerulonephritis associated with Staphylococcus aureus infective endocarditis: cases reports and mini-review of the literature**

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## Mini review

### Vasculitides and Glomerulonephritis associated with *Staphylococcus aureus* Infective Endocarditis: cases reports and mini review of the literature.

(2452 words)

Running title : Vasculitis/glomerulonephritis&*S.aureus*endocarditis.

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Abstract (186 words)

We reported two cases of *Staphylococcus aureus* Infective Endocarditis associated with vasculitides and glomerulonephritis respectively, before conducting an online search of previously published similar cases reports. Twenty five references were selected: 15 cases of glomerulonephritis; 2 cases of vasculitis and 8 cases involving both glomerulonephritis and vasculitis.

Vasculitides and glomerulonephritis associated with *Staphylococcus aureus* definite Infective Endocarditis **have been** reported since 1976. All cases except one described clinical symptoms occurring before or during initial antibiotics treatment. Except kidney, organs that were more frequently affected by vasculitis process were skin, gastrointestinal tract and peripheral nerve and the vessels involved were small to medium size vessels. When antineutrophil cytoplasmic antibodies were evidenced (6 out of the 25 cases (24%)), kidney was the most frequently affected organ. The most commonly observed pattern in Kidney biopsy was membranoproliferative glomerulonephritis with endocapillary proliferation sometimes associated with extra capillary crescents, whether or not antineutrophil cytoplasmic antibodies were evidenced. Right-sided Infective Endocarditis (especially in intravenous drug users) were overrepresented (14 of the 25 cases (56.0%)) in this review. Besides antibiotics, corticosteroids were the most frequently prescribed immunosuppressive treatment both for vasculitides or glomerulonephritis.

Keywords: *Staphylococcus aureus* ; Infective Endocarditis ; Glomerulonephritis ; Vasculitis.

Key messages :

- Vasculitides and glomerulonephritis associated with *Staphylococcus aureus* definite Infective Endocarditis **have been** reported since 1976.
- Except kidney, organs that were more frequently affected (by small to medium size vessel vasculitis) were skin, gastrointestinal tract and peripheral nerve.
- The most commonly observed pattern in Kidney biopsy was membranoproliferative glomerulonephritis with endocapillary proliferation and right-sided Infective Endocarditis (especially in intravenous drug users) were overrepresented in this review.

## Introduction

Infective Endocarditis (IE) due to *viridans group streptococci*, classically associated with symptoms suggestive of autoimmune diseases such as asthenia, joint pain, purpura, proteinuria, are becoming less frequent in developed countries (1).

Nowadays, *Staphylococcus aureus* is the leading cause of IE (1-3) mainly with acute onset and symptoms related to sepsis, heart failure or metastatic foci of infection (4). In such *Staphylococcus aureus* IE, symptoms suggestive of autoimmune diseases are so rare that they are almost not described even in large series of literature (2,5).

Herein, we reported two observations of *Staphylococcus aureus* IE associated with vasculitides and glomerulonephritis respectively, before we made a **descriptive** review of the literature focusing especially on vasculitides and glomerulonephritis associated with *Staphylococcus aureus* IE.

## Material and methods

### Case reports

#### *First case:*

A 27-year-old intravenous drug user (IVDU) was referred for asthenia, fever, dyspnea and cough evolving since several days. He had no significant past medical history. No crackles were heard on auscultation and rest of the physical examination was unremarkable except multiple cutaneous abscesses at the site of injections. C reactive Protein was 126 mg/L. Chest computerized tomography scan (CT scan) and transthoracic echocardiography evidenced multiple nodular opacities of both lung fields, sometimes excavated (figure 1A) and a 17 mm wide vegetation attached to the tricuspid valve respectively. Blood cultures grew Meticillin sensitive *Staphylococcus aureus* (MSSA) and the diagnosis of right-sided *Staphylococcus aureus* IE was made. Probabilistic antibiotherapy by Ceftriaxone was switched to intravenous Cloxacillin.

Six days after admission, despite negative blood cultures, multiple palpable purpuric lesions (sometimes necrotic) appeared on legs, feet soles and hands (figure 1B). Funduscopy was unremarkable. Creatinine blood level was within normal range and urinalysis did not detect significant proteinuria. HIV, Hepatitis B or C serologies and antinuclear, anti-native DNA and antineutrophil cytoplasmic (ANCA) antibodies were all negative. Rheumatoid factor was elevated in serum (96IU/mL); C4 complement level and total haemolytic complement assay were slightly lowered (0.19g/L (N>0.20g/L) and 59U (N>60U)

respectively) whereas C3 complement level was within normal range. Histopathological analysis of cutaneous purpuric lesion evidenced IgA and C3 deposited in the walls of small dermal blood vessels (figure 1B). No steroids therapy was initially prescribed for this small vessel cutaneous vasculitis associated with *Staphylococcus aureus* right sided IE but antibiotherapy by Cloxacillin was pursued.

Four days later (i.e ten days after admission), the patient complained of diffuse abdominal pain, nausea and vomiting. Upper gastrointestinal endoscopy performed showed ~~a normal gastric mucosa but~~ an inflammatory duodenal mucosa with circular shallow ulcerations and exsudation suggestive of vasculitis (fig1C). Superficial duodenal biopsy evidenced duodenitis but did not show small vessels vasculitis involving duodenum (fig 1C). Because gastrointestinal tract involvement was considered as a prognostic factor in systemic necrotizing vasculitides (6), a treatment by Prednisone 40 mg qd was here added to antibiotherapy during one month with 10 mg decrement each week. Outcome was favourable after Prednisone and Cloxacillin withdrawal, without clinical evidence for recurrence of digestive or cutaneous vasculitides up to 30 months later (fig 1D). Blood cultures and creatinine blood level remained sterile and within normal range respectively (fig 1E). Last echocardiography performed 3 months after the end of antibiotherapy evidenced a 3 mm wide residual vegetation attached to the tricuspid valve.

#### *Second case:*

A 74-year-old man was referred for low back pain evolving since 6 days despite Non Steroid Anti Inflammatory drugs. He was an orphan without knowledge of his biological parents but had no significant past medical history especially no renal disease history. He reported that he had had a small burn injury of third toe of the right foot 10 days before admission. His body temperature rose up to 39°C and clinical examination evidenced permanent back pain exacerbated by percussion of the last lumbar vertebra and associated with a leg pain suggestive of S1 radiculopathy. He had hollow feet and a slight atrophy of interosseous muscle of the hands (figure 2A). Electroneuromyography revealed a slowing of sensitive nerve conduction velocity and a decrease of amplitude of sensory nerve action potential of all tested nerves, suggestive of previously undiagnosed Charcot Marie Tooth disease. C reactive Protein was 221 mg/L. Blood and urine cultures grew MSSA and an antibiotherapy associating intravenous Cloxacillin and Gentamycin 3mg/kg qd was prescribed.

Two days after admission, the patient exhibited arthritis of right first metatarsophalangeal, right first metacarpotrapezoidal and right sternoclavicular joints.

Magnetic Resonance imaging showed T2 weighted sequence hyperintensity at the L3 and L4 vertebral bodies suggestive of spondylodiscitis, associated with posterior epiduritis. Bone scintigraphy evidenced also intense Technetium uptakes in the levels of C6-C7, T2-T3, T6-T7 discs but also right wrist, right first metatarsophalangeal, and right sternoclavicular joints (figure 2B). Transesophageal echocardiography evidenced 7mm wide vegetation attached to the aortic valve and the diagnosis of multiple osteoarticular infections complicating left-sided *Staphylococcus aureus* IE was made.

Three days later (i.e five days after admission), despite negative blood cultures, acute kidney injury occurred (creatinine blood level of 216 versus 76 $\mu$ mol/l on admission) after treatment by Non Steroid Anti Inflammatory, ~~then~~ gentamycin and ~~after~~ contrast enhanced thoracoabdominal CT scan performed the day before to rule out the presence of deep infectious foci. None was evidenced, but the patient developed also leg pitting oedema related to nephrotic syndrome, excluding the diagnosis of post contrast acute kidney injection. Urinalysis showed microhaematuria and proteinuria (2,4g/24h). Antinuclear, anti-native DNA, antineutrophil cytoplasmic and anti-glomerular basement membrane antibodies were all negative. Total haemolytic complement assay was slightly lowered (58U (N>60U)) whereas C3 and C4 complement levels were within normal range. Kidney biopsy was performed and biopsy specimen revealed 4 glomeruli (of which 1 was sclerosed), with endocapillary proliferation and IgA, IgG and C3 deposited throughout the mesangium and glomerular basal membrana, (Figure 2C). Oral corticotherapy by Prednisone 60 mg qd with progressive decrement during three months was added to antibiotic regimen consisting of six weeks of intravenous Cloxacillin and Levofloxacin and six weeks of oral Clindamycin and Levofloxacin. Outcome was favourable with a 24h proteinuria value of 700mg/24h and a creatinine blood level of 113  $\mu$ mol/L two months and one year after antibiotics and corticosteroids withdrawal respectively (fig 2D). The absence of haematuria in the following year after antibiotics and corticosteroids withdrawal allowed excluding idiopathic IgA nephropathy.

## Review

As stated above, vasculitides and glomerulonephritis are so rare that they are almost not described even in large series of literature (2,5). To ~~better describe~~ gather sufficient data for the description of vasculitides and glomerulonephritis associated with *Staphylococcus aureus* IE (VGaSAIE) that occurred in the previous years, we conducted an online search of cases reports. We screened cases reports previously published in English or French language in

Medline and Embase databases using keywords “*Staphylococcus aureus*” and “endocarditis” associated with “vasculitis” or “glomerulonephritis” or “purpura” without time limits. References were pooled with those obtained from a second search in Medline database only using keywords “endocarditis” and “glomerulonephritis”.

All title and/or abstracts of retrieved references were screened by 2 independent reviewers (AB and YN). Full text versions were obtained for references considered as relevant by both reviewers. Briefly, references were excluded if (i) these references corresponded to review, animal or experimental data or did not provide sufficient data about cases (ii) duplicate references (iii) unavailable references (with the exceptions of conference abstract) (iv) ~~these reference described vasculitides or glomerulonephritis associated with IE due to other bacteria than *Staphylococcus aureus*~~ (v) the diagnosis of *Staphylococcus aureus* IE could not be confirmed according to Dukes/Li criteria (7) (vi) all clinical or biological manifestations reported could be due to Sepsis or Septic Shock, secondary foci of infection, mycotic aneurysm, heart failure, or treatment (figure 3).

## Results

Twenty five references (8-32) were selected for review, whose results are shown in Table 1. Briefly, selected references described 15 cases of glomerulonephritis; 2 cases of vasculitis and 8 cases involving both glomerulonephritis and vasculitis.

## Discussion

### *Previous description of VGaSAIE:*

**The literature** review we performed allowed us to find cases quite similar to those we reported (12,20,22,23). These cases of VGaSAIE were observed since 1976 (8,9), before the emergence of *Staphylococcus aureus* as the leading cause of IE (1-3). Interestingly, older cases not fulfilling the diagnosis of *Staphylococcus aureus* IE according to Dukes/Li criteria (7) have been found during review references selection process (33,34). Even in the absence of genuine IE, these cases of *Staphylococcus aureus* bacteraemia with **abnormal** heart murmur (33,34) **occurring** before the first description of vegetation using echocardiography (35) could be linked to **similar** cases ~~reporting similar symptoms suggestive of autoimmune diseases and~~ associated with **bacteraemia or others infections due** to *Staphylococcus aureus* (36-39).

#### *Time delay between VGaSAIE and antibiotics treatment:*

All cases selected for review except one (17) described clinical symptoms occurring before or during initial antibiotics treatment, like those we reported. This temporal relationship and the favourable outcome with antibiotics (sometimes associated with surgery) but without immunosuppressive therapy (10,11,14,18,20,21,22,23,26,28) constituted a strong argument for a physiopathological link between *Staphylococcus aureus* IE and autoimmune process in the majority of cases. Conversely, the case reported by Hellmich and colleagues (17) described a microscopic polyangiitis occurring long after the end of antibiotics previously prescribed for *Staphylococcus aureus* IE. Microscopic polyangiitis resolved after immunosuppressive therapy only and this suggested more a self-evolving autoimmune process probably triggered by infection than an autoimmune process associated with IE. These two kinds of physiopathological patterns of VGaSAIE should not be compared, especially concerning therapy and outcome (see below) (17).

#### *Clinicobiological description of VGaSAIE:*

For these cases of autoimmune process associated with IE (8-16, 18-32), glomerulonephritis were more frequently reported than vasculitides in association with *Staphylococcus aureus* IE. Except kidney, organs that were more frequently affected by vasculitis process were skin, gastrointestinal tract (suggested by abdominal pain like the first case we reported) and peripheral nerve. The vessels involved were small to medium size vessels. To the best of our knowledge, no symptoms suggestive of large vessel vasculitis like those of giant cell arteritis have been described in *Staphylococcus aureus* IE, whereas such symptoms had previously been reported in Streptococcal Subacute Endocarditis (40-41). ANCA were evidenced in this review in 6 out of the 25 cases (24%), which is near the 18.3% rate (20 out of 109 cases) observed by Mahr and colleagues in a study focusing on the seroprevalence of ANCA in definite IE (42). When ANCA were evidenced, organs involved were mainly kidney (17,19,21,24,25,28) and anecdotally peripheral nerve and lung (19,21).

#### *Kidney biopsy pattern of Glomerulonephritis associated with Staphylococcus aureus infective endocarditis:*

The most commonly observed pattern in Kidney biopsy of glomerulonephritis associated with *Staphylococcus aureus* IE was membranoproliferative glomerulonephritis with endocapillary proliferation sometimes associated with extra capillary crescents, whether or not ANCA were evidenced (8-12,15,20,22,26,28). In such cases with available data (9-

12,20,22,28), deposits were made mainly of C3, IgA and/or IgG. These histopathological patterns (membranoproliferative glomerulonephritis with endocapillary proliferation sometimes associated with extra capillary crescents and C3, IgA and/or IgG deposits) were closer to those observed during all kind of *Staphylococcus aureus* infections (43) than those observed during IE (44). The exact physiopathological meaning of IgA deposits in the kidney during *Staphylococcus aureus* infections remained unknown (with the risk of confusion with IgA nephropathy and Henoch-Schönlein purpura nephritis) (43), whereas C3 and IgG deposits were presumed to be due to post-infectious and immune complex depositions process respectively (28,45). Taken together, these data suggested that histopathological pattern of kidney biopsy observed during glomerulonephritis associated with *Staphylococcus aureus* IE is not specific of IE (but rather of *Staphylococcus aureus* infection) and not specific either of a sole physiopathological mechanism.

#### *Immune complex deposition during VGaSAIE:*

Classically, immune complex deposition mechanism that was presumed to explain “extravalvular” manifestations of IE such as glomerulonephritis, was overrepresented in right-sided IE or IE evolving since more than one month (46). Interestingly, in this review focusing on VGaSAIE, right-sided IE accounted for 14 of the 25 cases (56.0%), which is far superior to the 23.6% rate (132 out 558 cases) observed in data focusing on all *Staphylococcus aureus* definite IE issued from the data of the International Collaboration on Endocarditis (2). This discrepancy is fully in line with data from Bayer and colleagues’ study (46), but we presume that right-sided IE (8,9,12-14,18,20,22,23,26-28) especially those occurring in intravenous drug user (IVDU) (8,9,12,14, 22,23,26) have been diagnosed late in the course of the disease, because of the lack of availability of routine echocardiography for older cases and probably because of delayed diagnosis in IVDU. Pre-hospital time delay evaluation in IVDU has not been addressed specifically in IE (47) but a longer time delay before diagnosis in IVDU is suggested by case reports focusing on infections other than IE (48). Taken together, we could hypothesize that right-sided IE especially in IVDU were overrepresented in this review focusing on VGaSAIE, because of a longer time delay before diagnosis, allowing (among other mechanisms) synthesis and deposition of immune complex leading to the development of glomerulonephritis or vasculitides, as suggested by the studies of Paccione and Bayer (26,46).

*Immunosuppressive treatment and outcome of VGaSAIE:*

In the review we performed, corticosteroids were the most frequently prescribed immunosuppressive treatment (17,19,24,25,27,29,32) both for vasculitides or glomerulonephritis. The outcome was favourable with corticosteroids for the sole patient who developed Glomerulonephritis and/or vasculitides after the end of Antibiotics (17), whereas only three out of the 6 patients who received corticosteroids for glomerulonephritis and/or vasculitides before or during antibiotics had favourable outcome (19,24,29), two died (25,27). There are no specific guidelines concerning the use of corticosteroids in IE associated with vasculitides or glomerulonephritis (7). In the literature, more data are available concerning the use of corticosteroids in glomerulonephritis ~~associated with IE~~ than in vasculitides associated with ~~others~~ IE or bacterial infections (49-51). Outcome was favourable in 3 out of 3 (49) and 5 out of 9 patients (50) receiving corticosteroids for glomerulonephritis respectively. The remaining four patients died in the latter study (50) and outcome was not defined specifically for the 7 patients who received corticosteroids for vasculitides in the study of Loricera and colleagues (51). Herein, corticosteroids appeared to be safe when blood cultures were sterile in the two cases we reported. Taken together, this suggested that corticosteroids should not be systematically proscribed in case of VGaSAIE. Physician could prescribe corticosteroids in this setting when they thought that benefit exceeded the risk. In the first case we reported, we prescribed corticosteroids because we considered that involvement of gastrointestinal tract (that is ~~involvement of another organ than heart considered as~~ a prognostic factor in systemic necrotizing vasculitides (6)) had a worse prognosis than right sided IE not requiring surgical treatment in a 27 year-old man without immunocompromised status and under antibiotics. (~~namely Kidney, Gastrointestinal tract or Central Nervous System~~) should lead in case of autoimmune damage mechanism (vasculitis or glomerulonephritis) to the prescription of corticosteroids. The evaluation of corticosteroids benefit/risk ratio may be more difficult in older patients like the second case we reported. Overall, among the 22 review patients with available outcome data, 5 died (22.7%) and 4 out of the 17 survivors had chronic renal failure. This seems consistent with previously described data of the literature focusing on glomerulonephritis associated with IE (50,52).

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Ref.	Sex (age) Drug user	Right sided (R) or left Sided (L) Infective Endocarditis	Clinical and biological manifestations suggestive of autoimmune diseases	Onset before (B), during (D) or after (A) antibiotherapy	Treatment	Outcome
(8)	M(32) IVDU	L&R	Purpura, ARF with microscopic haematuria. Necropsy: vasculitis involving skin, pericardium and lungs and membranoproliferative glomerulonephritis.	D	ATB	Died
(9)	M(40) IVDU	R	ARF with microscopic haematuria, proteinuria and low complement level Necropsy: membranoproliferative glomerulonephritis with C3 deposits and some epithelial crescents	D	ATB	Died
(10) 2/2	F(33)	L	ARF with microscopic haematuria, proteinuria, circulating immune complexes and low complement level Kidney Biopsy: membranoproliferative glomerulonephritis with C3 and IgG deposits	B	ATB + SURG	Cured
(11)	M(75)	L	ARF with microscopic haematuria, proteinuria and low complement level Kidney Biopsy: membranoproliferative glomerulonephritis with C3, C4 and IgG deposits and some epithelial crescents	D	ATB	Cured CRF
(12)	M(21) IVDU	R	Purpura, abdominal pain, microscopic haematuria, proteinuria and circulating immune complexes Skin Biopsy: leucocytoclastic vasculitis with IgA deposits Kidney Biopsy: membranoproliferative glomerulonephritis with C3, IgA and fibrinogen deposits and some epithelial crescents (15% glomeruli)	D	ATB	Cured Lost to follow up
(13)	F(35)	R	ARF with proteinuria and low complement level Kidney Biopsy : crescentic glomerulonephritis	D	ATB	Cured End stage CRF
(14)	F(38) IVDU	R	ARF with macroscopic haematuria, nephrotic range proteinuria circulating immune complexes	D	ATB	Cured
(15)	F(65)	L	Purpura, ARF, Acute motor axonal neuropathy Kidney Biopsy: membranoproliferative glomerulonephritis	B	ATB	Died
(16)	F(64)	L	Purpura, abdominal pain, Skin Biopsy: leucocytoclastic vasculitis	D	ATB	.
(17)	M(53)	L	Polyneuropathy, dyspnea with ground-glass appearance of the lung, microscopic haematuria, proteinuria, anti-MPO-p-ANCA Nerve Biopsy : necrotising vasculitis of the small vessels	A	CYC + CTC	Cured anti-MPO-p-ANCA titre decreased

(18)	F(40)	R	ARF with microscopic haematuria, proteinuria and low complement level Kidney Biopsy : crescentic glomerulonephritis with C3, C1q, IgG and IgM deposits	B	ATB	Cured
(19)	F(71)	L	Purpura, abdominal pain, mononeuritis multiplex, microscopic haematuria, anti-MPO-p-ANCA Skin Biopsy : necrotising vasculitis of small and medium sized arteries with fibrinoid necrosis and neutrophil infiltration	B	ATB + CTC	Cured with negative anti-MPO-p-ANCA
(20) 1/4	M(60)	R	ARF with microscopic haematuria, proteinuria and low complement level Kidney Biopsy: membranoproliferative glomerulonephritis with C3, IgA and IgG deposits	D	ATB	Cured
(21)	M(61)	L	Excavated pulmonary nodules, ARF, anti-MPO-p-ANCA	B	ATB	Cured
(22)	M(25) IVDU	R	ARF with proteinuria Kidney Biopsy: membranoproliferative glomerulonephritis with C3, C1q, IgA , IgM deposits and epithelial crescents (50-85% glomeruli)	B	ATB	Cured CRF
(23)	M(36) IVDU	R	Purpura, abdominal pain, ARF with microscopic haematuria Skin Biopsy: leucocytoclastic vasculitis with IgA deposits Kidney Biopsy: focal, segmental proliferative glomerulonephritis with C3 and IgA deposits	D	ATB + SURG	Cured
(24)	M(59)	L	ARF with microscopic haematuria, proteinuria, low complement level and anti-PR3-c-ANCA Kidney Biopsy : crescentic glomerulonephritis with C3, C1q, IgG and fibrinogen deposits	B	ATB + CTC	Cured with negative anti-PR3-c-ANCA CRF
(25) 3/3	M(65)	L	ARF with microscopic haematuria, proteinuria and anti-PR3-c-ANCA	D	ATB + CTC + IgIV	Died
(26)	M(23) IVDU	R	ARF with microscopic haematuria, proteinuria, low complement level Kidney Biopsy: membranoproliferative glomerulonephritis	B	ATB	Cured
(27)	F(68)	R	Purpura, low complement level Skin Biopsy: leucocytoclastic vasculitis	B	ATB + CTC	Died
(28)	M(42)	R	ARF with microscopic haematuria, proteinuria, low complement level and anti-PR3-c-ANCA Kidney Biopsy: membranoproliferative glomerulonephritis with C3 deposits	B	ATB + SURG	Cured anti-PR3-c-ANCA titre decreased
(29)	M(59)	L	Purpura, ARF with microscopic haematuria, proteinuria	B	ATB+ SURG+CTC	Cured
(30)	F(39)	R	ARF with microscopic haematuria, proteinuria	D	ATB + SURG+ PE	Cured
(31) 2/2	F(30)	R	ARF Kidney Biopsy : crescentic glomerulonephritis	D	ATB	.

(32)	M(63)	L	ARF with microscopic haematuria, proteinuria Kidney Biopsy : crescentic glomerulonephritis	B	ATB+CTC	.
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Table 1: Selected references.

Ref. reference and below reference number between parentheses, in italic the number of the case if more than one case was reported in this reference, M male, F Female, IVDU Intravenous Drug User, ARF Acute renal failure, ATB Antibiotherapy, SURG Heart Surgery, CTC Corticotherapy, AZA Azathioprine, CYC Cyclophosphamide, IgIV intravenous Immunoglobulins, PE Plasma exchange, CRF Chronic renal failure.

Overall, the outcome of 25 patients with *Staphylococcus aureus* Infective Endocarditis associated with Glomerulonephritis and/or vasculitides were described. The outcome was favourable (cure) with corticosteroids for the sole patient who developed Glomerulonephritis and/or vasculitides after the end of Antibiotics (17). Among the 24 patients who developed Glomerulonephritis and/or vasculitides before or during antibiotics, 6 received corticosteroids. Three out of 6 were cured (one with chronic renal failure) (19,24,29), 2 died from sepsis 28 and 50 days after admission respectively (25,27) and outcome was not described for the last patient (32).

Figure captions:

Figure 1: **A.** Chest Computerized Tomography scan showing multiple nodular opacities of both lung fields, sometimes excavated. **B.** Multiple palpable purpuric lesions appeared on legs, feet soles and hands. Lower left panels: Histopathological analysis of cutaneous purpuric lesion (immunofluorescent assay) evidencing IgA and C3 deposited in the walls of small dermal blood vessels. **C.** Upper gastrointestinal endoscopy showing an inflammatory duodenal mucosa with circular shallow ulcerations and exudation. Lower panel: Histopathological analysis of superficial duodenal biopsy (Hematoxylin, Eosin, Saffron staining, X20) evidencing duodenitis but no small vessels vasculitis. **D.** Sequelae of purpuric eruption on hands without evidence for new lesions 6 (left) and 10 (right) weeks later. **E.** Time evolution of creatininemia, day 1 corresponding to the day of hospitalisation.

Figure 2: **A.** Hollow feet and atrophy of interosseous muscle of the left hand. **B.** Bone scintigraphy evidencing intense Technetium uptakes in the levels of C6-C7, T2-T3, T6-T7 discs, right wrist, right first metatarsophalangeal, and right sternoclavicular joints. **C.** Left: Histopathological analysis of Kidney Biopsy evidencing 1 glomerulus with endocapillary proliferation (Masson's trichrome, X40). Right: Histopathological analysis (immunofluorescent assay) of Kidney Biopsy evidencing IgA deposited throughout the mesangium of 1 glomerulus. **D.** Time evolution of creatininemia (left) and proteinuria (right), day 1 corresponding to the day of hospitalisation.

Figure 3: Flow Chart of references selection.