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REVIEW

Urological manifestations and treatment of the primary systemic vasculitides

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Abstract

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying size and multiple organs. Urological manifestations of PSV are uncommon. Testicular vasculitis is the most commonly reported finding and is associated with Polyarteritis Nodosa (PAN), Henoch-Schönlein Purpura (HSP), anti-neutrophil cytoplasm antibody associated Vasculitides (AAV), Giant Cell Arteritis (GCA) and Kawasaki disease. Prostatic vasculitis has been reported in association with GCA and AAV. Ureteric involvement has been noted in PAN, HSP and AAV. Other urogenital manifestations of PSV include genital ulceration and bladder dysfunction in Behçets Disease and haematuria which is commonly seen in many of the PSV. Finally, therapies used to treat the PSV, especially cyclophosphamide, are associated with urological side-effects including haemorrhagic cystitis and urothelial malignancy. The aim of this review is to examine how the urological system is involved in the PSV. Each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management. Identification of urological manifestations of PSV is important as in many cases symptoms may improve with immunosuppressive therapy, avoiding the need for invasive surgery. Additionally, patients who present with isolated urogenital PSV are at higher risk of developing subsequent systemic vasculitis and will need to be followed up closely.

Key words: Urology; Vasculitis; Takayasu arteritis; Giant cell arteritis; Polyarteritis Nodosa; Kawasaki disease; Henoch-Schönlein Purpura; Anti-neutrophil cytoplasm antibody associated vasculitides; Granulomatosis with polyangiitis; Microscopic polyangiitis; Behcets disease; Eosinophilic granulomatosis with polyangiitis; Epididymo-orchitis; Prostatitis; Ureteric stenosis

Core tip: Urogenital manifestations of primary systemic vasculitides are rare. Patients will usually have other systemic signs and symptoms to suggest an underlying vasculitic process. Inflammatory markers including erythrocyte sedimentation rate and C-reactive protein are often raised and specific auto-antibody testing may be useful in identifying the underlying diagnosis.

If an underlying vasculitic process is suspected, early involvement of a specialist is essential. Symptoms usually improve with immunosuppressive therapy and may avoid the need for invasive surgery. Patients who present with isolated single-organ vasculitis of the urogenital tract will need to be followed up closely in case they subsequently develop systemic disease.

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INTRODUCTION

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying sizes and multiple organs. The PSV are classified according to the size of vessel they predominantly affect. Nomenclature and detailed definitions for each of the PSV were set out by the Chapel Hill Consensus Conference (CHCC) in 1994 and reviewed again in 2012[1]. In this review each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management (Table 1). It should however be borne in mind that the treatments for these diseases change and improve over time and management of these rare diseases should be undertaken in collaboration with a specialist with appropriate expertise.

LARGE VESSEL VASCULITIDES

Takayasu arteritis

Takayasu arteritis (TA) is a rare, systemic, large-vessel vasculitis of unknown aetiology. It is defined by the CHCC as "granulomatous inflammation of the aorta and its major branches". TA occurs most commonly in Mexico, Japan and parts of Asia, predominantly in women of childbearing age. It is classified depending on the specific part of the aorta that is affected. Complications of disease include stroke, seizures, hypertension and retinopathy. Treatment is usually with immunosuppression to control inflammation but if vessels become fibrosed and stenotic, angioplasty +- stenting and bypass grafting may be necessary[2,3].

No specific urological manifestations of TA have been reported in the literature. There are a few isolated case reports of retroperitoneal fibrosis causing obstructive uropathy in association with TA. In the acute setting this was managed with ureteric stents and long-term improvement in symptoms was noted with immunosuppressive therapy[4-6].

Giant cell arteritis

Giant cell arteritis (GCA) is a large vessel vasculitis characterized by granulomatous inflammation predominantly affecting the thoracic aorta and its branches.

Epidemiology and clinical features: It is predominantly a disease of older people with the highest incidence in patients 70-80 years of age. The incidence of disease is also highest in patients of Northern European, North American or Scandinavian descent[7].

Constitutional symptoms such as fever, fatigue and weight loss are common in GCA as are specific manifestations of the disease include headache, scalp tenderness, jaw claudication and visual disturbance. Approximately 20% of patients will manifest clinical signs of large vessel involvement, including aneurysmal and stenotic lesions of the abdominal aorta[8].

Treatment and prognosis: The mainstay of treatment in GCA is with high dose corticosteroids to induce disease remission. Methotrexate may be used as adjunctive therapy, whilst TNF inhibitors and the IL-6 inhibitor, tocilizumab, may have a role in the treatment of relapsing and refractory disease[9,10].

The most serious complication in patients with GCA is blindness secondary to ischaemic optic neuropathy, which develops in approximately 7%-14% of all patients. As a result, patients often receive prolonged courses of steroids, with an average duration of therapy of two years. Side effects from long-term steroid therapy, include hypertension, diabetes and osteoporosis[11].

Urological manifestations: Urological manifestations of GCA are seldom reported. Epididymal involvement has been reported in a 66-year-old male with a 3 mo history of generalised fatigue, right sided epididymal tenderness, raised inflammatory markers and a normochromic normocytic anaemia. Epididymal biopsy demonstrated chronic inflammatory cell infiltration and the presence of "giant cells". The patient subsequently underwent a temporal artery biopsy, which confirmed the diagnosis of giant cell arteritis. This patient responded well to high dose corticosteroids[12].

Testicular involvement has also been reported in a 76-year-old male with weight loss, malaise and right testicular swelling. His ultrasound scan was suggestive of testicular malignancy and he underwent radical orchidectomy. The excised specimen showed a shrunken testis surrounded by dense, focally calcified tissue, up to 7 mm thick with patchy intimal thickening of the spermatic cord and a chronic inflammatory cell infiltrate in the vessel walls. One arteriole showed a focus of destructive arteritis with the presence of giant cells[13].

MEDIUM VESSEL VASCULITIDES

Polyarteritis Nodosa

Polyarteritis Nodosa (PAN) is a rare necrotising systemic

Table 1 Summary of the urogenital manifestations of the primary systemic vasculitides, defined according to the Chapel Hill Consensus Criteria

Primary systemic vasculitides		Urogenital manifestations
Large vessel	Takayasu arteritis	Obstructive uropathy secondary to retroperitoneal fibrosis
	Giant cell arteritis	Epididymo-orchitis
Medium vessel	Polyarteritis Nodosa	Orchitis, ureteric stricture, haematuria, glomerulonephritis, spontaneous peri-renal haemorrhage
	Kawasaki's disease	Orchitis, ureteric stricture
Small vessel	Antineutrophil cytoplasmic antibody associated vasculitis	
	Microscopic polyangiitis	Glomerulonephritis, prostatitis
	Granulomatosis with polyangiitis (Wegener's)	Glomerulonephritis, prostatitis, orchitis, ureteric stenosis, penile ulceration, necrotizing urethritis, large renal and bladder granulomas ("pseudotumours")
	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Prostatitis, ureteric stricture, urethral ulceration
	Immune complex small vessel vasculitis	
	Anti-glomerular basement membrane disease	Glomerulonephritis, haematuria
	IgA vasculitis (Henoch-Schonlein)	Glomerulonephritis, haematuria
	Cryoglobulinaemic vasculitis	Glomerulonephritis, haematuria, epididymo-orchitis, ureteric strictures, bladder wall hematoma, haemorrhagic cystitis, penile and scrotal pain and swelling, priapism, spermatic vein thrombosis
	Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)	Glomerulonephritis, haematuria
Variable vessel	Behçets disease	Genital ulceration, epididymitis, sterile urethritis, bladder wall ulceration, cystitis, vesico-vaginal fistula, neuropathic bladder
	Cogan's syndrome	Nil

vasculitis typically affecting medium and small sized arteries. Inflammation usually targets muscular arteries at bifurcations or branch points. The inflammatory lesions start at the vessel intima and may progress to involve the entire arterial wall, destroying the internal and external elastic lamina and resulting in fibrinoid necrosis. The weakened vessel walls are prone to aneurysm formation and subsequent rupture, haemorrhage and thrombosis. During the healing process medial and intimal proliferation may result in occlusion of vessels, leading to tissue ischaemia or infarction[14].

Glomerulonephritis and pulmonary involvement are not usually a feature of PAN, as there is characteristic sparing of smaller blood vessels including arterioles, capillaries and venules[1].

PAN may be idiopathic or secondary to specific viral triggers, the most common of these being Hepatitis B viral (HBV) infection but rare associations with hepatitis C virus and HIV have been reported[15,16]. Patients may display a wide variety of clinical presentations from limited single organ disease to widespread fulminant multi-organ failure.

Epidemiology: PAN is a rare disease. Accurate estimation of incidence and prevalence rates are difficult and largely dependent on the disease classification method used. Reported annual incidence of PAN in most developed countries is estimated between 2-9 cases/million population/year[17-19], with overall prevalence of the disease estimated at approximately 30 cases/million population in France[20]. PAN can affect patients of any age, ethnicity or gender but a peak in incidence has been consistently noted in the 5th and 6th decades of life. Males are also more commonly affected than females[21].

Over the past 20 years PAN has become less common. This may be due to a reduction in the number of PAN cases secondary to HBV infection, falling from approximately one third of all cases to 7%-10% in more recent estimates[22] which may be secondary to widespread HBV vaccination of high risk groups and screening of blood products[23]. The reduction in PAN cases may also be due to re-classification of a number of other necrotising systemic vasculitides, which were previously grouped together as PAN, including Microscopic polyangiitis (MPA) and cryoglobulinaemic vasculitis.

Clinical features: Patients typically present with systemic symptoms including malaise, weight loss and fever. The kidneys, skin, joints, muscles, nerves, and gastrointestinal tract are commonly involved (Table 2)[21].

Classification and diagnosis: There is no specific serological test for PAN and a combined assessment of clinical, angiographic and biopsy findings are usually required for diagnosis. Angiographic evaluation is key to this process with conventional arteriography remaining a "gold standard" despite MRI and CT being increasingly used for this purpose. Typical findings are multiple small aneurysms (< 1 cm) which are most commonly seen in the distribution of the renal and mesenteric arteries, although these are not pathognomic for PAN[24]. Biopsy findings include the presence of transmural non-granulomatous necrotising inflammation in medium sized arteries[25]. Areas most likely to be biopsied are those easily accessible

Table 2 Main clinical manifestations of patients with polyarteritis nodosa[7,14]

Manifestation	Specific problems	Frequency
Systemic symptoms	Fever, malaise, weight loss, myalgias arthralgias	80%
Neuropathy	Mononeuritis multiplex, polyneuropathy	75%
Arthralgias and/or myalgias	Articular and/or diffuse extremity pain	60%
Cutaneous	Livedo reticularis, purpura, ulcers	50%
Renal disease	Elevated creatinine, haematuria, proteinuria	50%
Gastrointestinal symptoms	Abdominal pain, nausea/vomiting, diarrhoea rectal bleeding, ulceration, peritonitis	40%
Hypertension	New onset	35%
Central nervous system disease	Stroke, confusion	20%
Orchitis	Testicular pain, swelling	20%
Cardiac involvement	Cardiomyopathy, pericarditis, palpitations, myocardial infarction	10%
Peripheral vascular disease	Claudication, ischaemia, necrosis	10%
Ophthalmological	Exudates, vasculitis	10%

including, sural nerve, muscles and testes[26,27].

Classification of PAN was published by the American College of rheumatology (ACR) in 1990[28]. This classification lists the following typical signs and symptoms of PAN: (1) Livedo reticularis; (2) Testicular pain or tenderness; (3) Myalgia (excluding that of the shoulder hip and girdle) or weakness; (4) Mononeuropathy or polyneuropathy; (5) New onset rise in diastolic blood pressure > 90 mmHg; (6) Elevated levels of serum blood urea nitrogen (> 40 mg/dL or > 14.3 mmol/L) or creatinine (> 1.5 mg/dL or > 132 mmol/L); (7) Evidence of hepatitis B virus infection *via* serum antibody or antigen serology; (8) Characteristic arteriographic abnormalities not resulting from non-inflammatory disease processes; and (9) A biopsy of medium or small sized artery containing polymorphonuclear cells.

According to the ACR criteria, the presence of at least 3 of these features is required for classification of disease as PAN with 82% sensitivity and 87% specificity rate.

Treatment and prognosis: Previously, untreated PAN was fatal in weeks to months in approximately 50% of patients. The five year survival rate was as low as 13%. In 1996 the French Vasculitis Study Group (FVSG) analysed data from a prospective study of 346 patients with PAN and eosinophilic granulomatosis with polyangiitis (EGPA) and identified five factors that were associated with poor prognosis. These factors are: (1) Renal Involvement-Proteinuria > 1 g/24 h; (2) Renal Impairment-Serum creatinine > 1.5 mg/dL; (3) Gastrointestinal Involvement-Presence of bleeding, perforation, infarction or pancreatitis; (4) Neurological Involvement; and (5) Cardiac involvement-Presence of cardiomyopathy.

These factors were adapted into a prognostic "Five Factor Score" (FFS) system. The presence of any one of these five factors is associated with poor prognosis and increased mortality[29]. When the FFS is zero, the predicted mortality rate at 5 years is 11.9%. When the FFS is 1, the mortality rate is 25.9%, and when the FFS is 2 or more, the mortality rate is as high as 45.9%.

Trials conducted by the FVSG suggest that corticosteroids alone are adequate first line therapy for patients with PAN with a FFS of zero although 40% may require additional immunosuppression[30]. Patients with a FFS $\geqslant$ 1 should receive intermittent intravenous cyclophosphamide in addition to corticosteroids[31]. For cases of HBV associated PAN, antiviral therapy, including vidarabine, lamivudine and interferon alpha 2-b, may be added to corticosteroid therapy, with or without plasma exchange[32,33].

Urological manifestations: Urogenital manifestations are reported more commonly in patients with PAN secondary to HBV infection than in patients with primary PAN[34]. Autopsy data from patients with PAN confirms testicular involvement in 38%-86% of cases. Of these patients only 18% will manifest any clinical signs and symptoms[35]. Testicular involvement may be part of a spectrum of systemic involvement or in rare cases it may be an isolated presentation of the disease. It is not unusual to see unilateral testicular involvement as part of a spectrum of systemic disease. Symptoms of testicular involvement are hugely variable, ranging from completely asymptomatic to severe pain, swelling, erythema and/or a local mass, with one isolated case report of asynchronous bilateral complete testicular necrosis in association with PAN[36]. This clinical picture often leads to a misdiagnosis of acute orchitis, torsion or neoplasm. As laboratory data and radiological findings are often non-specific in these cases, histological analysis of biopsy specimens remains the mainstay of diagnosis. Testicular biopsies in PAN commonly reveal transmural necrotising arteritis with focal infarcts and haemorrhagic lesions, vasculitis of testicular and epididymal arteries is commonly noted[36-45].

Corticosteroid therapy, with or without cyclophosphamide in refractory cases, has good outcomes for testicular symptoms in PAN. Length of therapy and dosage will vary in each individual case[37,38,46]. Current consensus is that orchidectomy is the treatment of choice in cases of isolated single-organ testicular

PAN. In many of these cases exclusion of a testicular neoplasm is difficult on the basis of clinical findings and the safest option is to remove the testicle. Close follow up and monitoring of these patients is also essential to rule out subsequent development of systemic PAN, although analysis of case reports show that this has rarely been reported[39].

There are a number of case reports describing ureteral strictures in polyarteritis nodosa[47-55]. The finding of imprints on the ureteral wall or a nodular appearance of the ureter, simulating a string of pearls, on an excretory urogram, are suggested to be pathognomonic for this disorder[51]. In the majority of these cases resolution of the stricture was achieved with systemic therapy for PAN but in isolated cases, resection of the stenosed ureteric segment became necessary[49].

There is a single case report of a patient with hepatitis B-associated PAN presenting with bilateral hydronephrosis in the absence of an obstructive lesion. It was presumed that vasculitis-related myopathy or neuropathy of the ureter was the most likely cause of this finding. The patient was treated with high-dose steroids, cyclophosphamide, and plasmapheresis with successful resolution of the hydronephrosis and resolution of acute kidney injury[56].

Kidneys are commonly affected in PAN. Luminal narrowing of inflamed renal arteries leads to glomerular ischemia but not inflammation or necrosis. Urinalysis in PAN, when abnormal, tends to show shows sub-nephrotic range proteinuria and microscopic hematuria. Red blood cell casts (indicative of a glomerular focus of inflammation) are usually absent. In patients with red blood cell casts, alternative diagnoses should be considered, including anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis or systemic lupus erythematosus.

Aneurysm formation of renal arteries in PAN may lead to life-threatening spontaneous peri-renal haemorrhage (SPH). In a meta-analysis of 165 cases of SPH, PAN was the reported cause in 12% of patients and is the most likely cause in patients with bilateral SPH[57]. The typical clinical presentation is of a patient with loin pain and a peri-renal mass, in combination with hypotension and a significant fall in haemoglobin. Rapid recognition of this condition and emergency resuscitation is essential. CT angiogram is the imaging modality of choice and endovascular management, such as percutaneous transcatheter embolisation is used with increased frequency to deal with ruptured visceral artery aneurysms associated with PAN[58]. In some cases the haemorrhage resolved with conservative therapy and observation but in other cases surgical evacuation of the haematoma or partial/complete nephrectomy was necessary[57].

KAWASAKI DISEASE

Kawasaki disease (KD) or "Mucocutaneous Lymph Node Syndrome" is an acute medium-vessel vasculitis syndrome of early childhood.

Epidemiology and clinical features: KD is one of the commonest vasculitides in early childhood, with the majority of cases occurring in patients less than 5 years of age and a peak in incidence occurring at approximately 30 mo of age. There is significant geographical variation in the incidence of KD with the majority of cases occurring in East Asia[59].

Diagnosis of KD is confirmed by the presence of fever for > 5 d and four of the following American Heart Association diagnostic criteria, listed below[60]: (1) Bilateral conjunctival injection; (2) Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue; (3) Polymorphous rash; (4) Changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation; and (5) Cervical adenopathy.

KD is a self-limiting disease, lasting for an average of 10-12 d without treatment. However coronary artery aneurysms develop in 20%-25% of cases with significant morbidity and mortality if untreated[59].

Urological manifestations: Urogenital involvement in KD is extremely rare, described in two isolated case reports. A six year old boy presented with typical symptoms of KD and it was incidentally noted that he had pain and swelling of his left testicle, in keeping with epidiymo-orchitis. The inflammation settled over the next few weeks with symptomatic treatment only and at six weeks follow up there were no persisting abnormalities. A second case report describes a seven year old boy with a one week history of cough, neck pain and swelling, fever and vague abdominal pain. He was diagnosed with KD and subsequently developed left sided pelvi-ureteric junction obstruction. Initially he was treated conservatively but due to worsening hydronephrosis, a nephrostomy was inserted and immunoglobulin therapy initiated. Subsequent scans confirmed an inflammatory stricture at the level of the left pelvi-ureteric junction. The stricture was surgically excised and a left sided dismembered pyeloplasty was performed. The patient subsequently recovered normal function of the left kidney and pelvi-calyceal system. The excised section of ureter showed findings in keeping with vasculitis[61,62].

Management: As KD is a self-limiting illness, the aim of therapy is to limit cardiovascular morbidity and mortality. Patients are treated with aspirin and intravenous immunoglobulin, as the addition of intravenous immunoglobulin has been shown to reduce the incidence of coronary artery complications compared with aspirin alone[63].

SMALL VESSEL VASCULITIS

ANCA associated vasculitis

AAV are multisystem necrotising small vessel vasculitides

of unknown cause. Included in this group are: (1) Granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis); (2) MPA; and (3) Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome).

The AAV are a group of rare disorders, with varying estimates of incidence and prevalence worldwide. In the United Kingdom reported incidence is estimated at 10.3/million population/year (GPA), 8.9/million (MPA) and 3.7/million (EGPA)[17]. There is a peak in incidence in the 7th and 8th decades of life[64].

Clinical features and diagnosis: Constitutional symptoms such as fever, malaise, anorexia, myalgia and weight loss are common in AAV.

Granulomatosis with polyangiitis

In GPA, necrotising granulomatous inflammation most commonly affects the upper and lower respiratory tract and kidneys. Upper respiratory tract symptoms include rhinorrhoea, epistaxis, sinusitis, otitis media, collapse of the nasal bridge, and tracheal stenosis. Lung involvement in GPA usually presents with cough, haemoptysis, and dyspnoea and can progress to life-threatening pulmonary haemorrhage. Rapidly progressive crescentic glomerulonephritis is also common. GPA may also affect the eyes; the bowel, causing ischemia and haemorrhage; the heart, causing myocardial ischemia, and the peripheral nervous system, causing mononeuritis multiplex[65,66].

MPA

MPA is clinically very similar to GPA, except there is no granuloma formation and upper respiratory tract involvement is rare. Renal involvement is very common, and pulmonary haemorrhage can also occur[66].

EGPA

EGPA, is characterized by eosinophilia, asthma, and necrotizing vasculitis. Vasculitis can affect the skin, peripheral nerves, muscles, and the intestine. Renal involvement is usually mild, and severe renal failure is uncommon[67].

Diagnostic tests

The diagnosis of ANCA-associated vasculitis is made using a combination of clinical findings, biopsies from relevant involved organs (typically kidney, nasal mucosa, or occasionally lung) and the presence of ANCA autoantibodies. ANCA autoantibodies may be directed against the neutrophil enzymes proteinase-3 (PR3) and/or myeloperoxidase (MPO). These specific ANCAs can be detected by enzyme-linked-immunosorbent assays (ELISA). Initial screening for detection of ANCA antibodies is by indirect immunofluorescence (IIF), prior to antigen specific ELISAs. ANCA detected by IIF are described as having a cytoplasmic (cANCA) or perinuclear (pANCA) pattern. cANCA found by IIF usually corresponds to anti-PR3 on ELISA and pANCA to anti-MPO. cANCA is seen in 81% of GPA patients and less commonly in MPA and EGPA. pANCA are detected in 65% of patients with MPA and less commonly in GPA and EGPA. In patients with clinical symptoms suggestive of these diseases, a combination of cANCA and positive PR3 ELISA has a positive predictive value (PPV) for GPA of nearly 100% but a sensitivity of only 69%. pANCA and MPO positive ELISA has a PPV of 47.5% for MPA and a specificity of 99.5%[68].

Treatment and prognosis: Although previously almost universally fatal the current five-year survival is approximately 80%. Early morbidity and mortality are mainly due to side effects of immunosuppressive therapy[69].

Treatment consists of two phases. Remission induction (3-6 mo) followed by maintenance of remission (at least 18 mo) to prevent disease relapse. Corticosteroids and cyclophosphamide are most commonly used to induce remission although there may be a role for methotrexate in more limited disease and rituximab in refractory cases and patients with a contraindication to cyclophosphamide. In order to minimise cyclophosphamide toxicity, patients are usually changed to azathioprine or a suitable alternative for maintenance therapy[70-72].

Urological manifestations: Renal involvement is common in GPA and MPA. In studies from the National Institute of Health in the United States, glomerulonephritis (GN) was present in 18% of patients at the time of presentation and subsequently developed in 77% to 85% of patients, usually within the first two years of disease onset. Patients with active GN and AKI will have haematuria and glomerular red cell casts. Cases of intermittent asymptomatic haematuria in association with normal renal function have also been reported.

Lower urogenital tract involvement in AAV is not commonly reported. Of the reported cases, the majority are in association with GPA.

Approximately 2.3%-7.4% of GPA patients will suffer from urogenital manifestations of the disease. The prostate is the most commonly involved organ but the ureters, testes, epididymis, seminal vesicles and penis may also be affected.

Prostatis secondary to GPA may present with dysuria, haematuria or bladder outflow tract obstruction and urinary retention. A combination of histopathological and serological tests are usually necessary to confirm the diagnosis. Resolution of symptoms is successfully achieved in most patients with medical therapy alone[65,73-87].

In a study of 72 male patients with testicular vasculitis, GPA was the second most common diagnosis, after PAN. Approximately 17% of all cases of isolated testicular vasculitis were due to GPA. As with other

forms of testicular vasculitis, patients may present with testicular pain, erythema, swelling or a localised mass. Ultrasound imaging may demonstrate multiple hypo-echoic areas and impaired blood flow. Diagnosis is usually confirmed with serological testing for ANCA autoantibodies and testicular biopsy, demonstrating granulomatous necrotising inflammation. Therapy with corticosteroids and immunosuppressants is reported to result in rapid resolution of symptoms[88-94].

Ureteric stenosis has also been reported in patients with GPA. Ureteric stents may be required in the short-term to relieve acute obstructive uropathy. Systemic therapy with immunosuppressants is usually successful in treating the inflammatory ureteric lesions but surgical intervention may become necessary[78,95-98].

There are a few case reports describing aggressive penile ulceration, which may become necrotic, in association with GPA. It is a rare, but important differential diagnosis, for penile lesions in the elderly population[78,99-104]. There are also a few case reports describing aggressive necrotising urethritis in both male and female elderly patients. This form of destructive urethritis may mimic invasive urethral carcinoma, but may respond well to immunosuppression[102,105,106].

Rarely patients with GPA present with large granulomas of the kidney and bladder or "pseudotumours". Radiologically these lesions mimic malignant tumours but immunosuppressive therapy usually results in a rapid reduction in the size of these masses[78,93,107,108].

There are two isolated case reports of prostatic involvement with MPA. In both cases 79-year-old males who presented with fever, malaise, weight loss and a cough. One had interstitial pneumonitis and the other a small mass in the left lower lobe of the lung. In both urinalysis revealed non-visible haematuria and serum prostate specific antigen (PSA) was elevated. In the first case prostate biopsy demonstrated fibrinoid degeneration with vasculitic changes involving the arterioles. In the second, prostate biopsy revealed changes consistent with vasculitis. Both had detectable serum MPO-ANCA. Both patients responded well to corticosteroids and cyclophosphamide[109,110].

Prostatic involvement is also reported in EGPA. In one a 74-year-old male, who had previously been treated for asthma, underwent transurethral resection of the prostate. Post-operatively he developed pyrexia and eosinophilia. The biopsy specimens showed eosinophilic prostatitis in keeping with EGPA. The patient's symptoms responded to oral prednisolone[111].

Ureteric obstruction secondary to calcification and stenosis has been reported in a 19-year-old male with multiple bowel perforations due to EGPA. Initially nephrostomies were inserted and subsequent ureteroscopy revealed multiple ureteral stones and dystrophic calcification within the ureteric walls. The obstruction was managed with repeated ureteroscopy and ureteric stent insertion with preservation of renal function[112].

A 33-year-old male with known EGPA presented ulceration of the mid-penile urethra. Biopsy showed chronic inflammation with infiltration of eosinophils as well as granulomas, giant cells and histiocytes and a thick walled blood vessel. This was occluded and infiltrated with inflammatory cells indicating active vasculitis. The patient responded well to intermittent intravenous cyclophosphamide with corticosteroids[113].

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP), also known as IgA vasculitis, anaphylactoid purpura and purpura rheumatica, is a systemic inflammatory disorder of small vessels characterised by IgA immune complex deposition and leukocytoclastic vasculitis. Skin, joints, bowel and kidneys are the most commonly affected organs.

Epidemiology

HSP is the commonest form of systemic vasculitis in childhood. Seventy five percent of all HSP cases involve children aged 2-11 years. The incidence of HSP in children < 17 years has been variously reported between 10-20 per 100000 population per year, with a peak in incidence between 5-7 years of age[114-116]. Exact incidence of adult HSP is not known but it is relatively rare and known to follow a more severe course, with a higher incidence of renal impairment and end-stage renal disease[117,118].

Clinical features and classification

Clinical Features of HSP typically include prodromal symptoms including headache, fever and anorexia. The hallmark of disease is the presence of a palpable purpuric rash in the absence of thrombocytopaenia or coagulopathy. This rash is typically found on the lower limbs and buttocks and less commonly on the upper limbs. This rash is present in almost all cases of HSP and is the presenting feature in over half of all patients[119]. The rash may be accompanied by arthralgia, especially of the knees and ankles, in up to 80% of cases[119,120].

Gastrointestinal manifestations of the disease are common, including colicky abdominal pain and vomiting, diarrhoea, GI bleeding, intussusception, infarction, strictures, perforation, fistula formation, gall bladder hydrops and acute appendicitis[121].

Renal disease occurs in approximately half of all patients. Haematuria and significant proteinuria are common and renal biopsy may demonstrate a diffuse or focal segmental mesangioproliferative pattern of glomerulonephritis. HSP nephritis may lead to progressive chronic kidney disease. Approximately 1%-5% of patients will develop end stage renal failure[120,122].

Urological manifestations of HSP

A wide variety of urogenital manifestations of HSP have been reported in the literature. This includes: (1)

Haematuria (visible and non-visible); (2) Unilateral or bilateral ureteritis with associated stenosis and hydronephrosis[123]; (3) Bladder wall hematoma[124]; (4) Haemorrhagic Cystitis[125]; (5) Painful swelling of the scrotum and penis[126,127]; (6) Epididymo-orchitis or orchitis[128-133]; (7) Priapism[134]; and (8) Thrombosis of the spermatic veins[135].

Many of the above complications are rare and have only been described in isolated case reports.

Haematuria is a common feature of the disease. A prospective study of 250 patients noted that 85% of patients had non-visible haematuria at the time of presentation and a further 10% had visible haematuria[118].

Scrotal and testicular involvement are the commonest lower urogenital tract manifestations of HSP and are reported in approximately 13% of cases. Clinical findings include pain, tenderness, and swelling of the involved testicle and/or scrotum. Occasionally, testicular symptoms may precede the development of a rash and may be the first presentation of disease[136]. There is only one confirmed case of testicular torsion in HSP[137].

Diagnosis

Diagnosis of HSP in childhood is primarily clinical. In adults a skin or renal biopsy may be performed. Serum IgA is raised in 50% of cases and autoantibodies that are present in other forms of vasculitis are usually absent[122]. Radiology, especially ultrasound evaluation, may be useful for identifying GI complications of disease including bowel wall thickening, intussusception and haematomas[138]. Similarly ultrasound examination of the scrotum and testicle is useful to assess for suspected epididymo-orchitis. Additionally Doppler flow studies and technetium Tc99m radionuclide scanning can aid in ruling out testicular torsion. In cases of torsion, these studies demonstrate decreased blood flow to the testicle, in contrast to the normal or increased flow seen in HSP[136].

Treatment and outcomes

HSP is typically an acute and self-limiting illness, usually lasting less than four weeks. Short-term morbidity is dependent on the presence and severity of gastrointestinal involvement and long-term prognosis is dependent on the extent and chronicity of renal involvement[121]. There is no form of therapy that has been found to shorten the duration of HSP and the focus of therapy therefore remains supportive, ensuring adequate hydration and analgaesia. There is no convincing evidence at present to suggest that corticosteroid therapy will reduce the risk of developing serious renal or gastrointestinal complications of the disease or that it will significantly shorten the duration of illness. Use of corticosteroids may however be considered in cases of persistent nephritic syndrome, with significant crescent formation or alternatively in patients with severe abdominal pain, GI haemorrhage, significant soft tissue or scrotal oedema or neurological involvement[139-142]. In severe and resistant cases of HSP, additional immunosuppressive agents and plasmapheresis may be considered[143-145].

Testicular and epididymal disease in HSP is usually self-limiting and resolves in a matter of days with conservative management. Corticosteroid therapy may be indicated in patients with severe testicular pain and swelling which is slow to improve or in cases accompanied by severe systemic symptoms[146]. In the isolated case report of a patient with spermatic vein thrombosis, treatment with low molecular weight heparin was required[135]. Anecdotal evidence in those patients presenting with ureteritis and associated stenotic lesions suggest that some cases are self-limiting and in other cases complete resolution was noted with a course of corticosteroids. In a few cases though, residual stenotic lesions and subsequent urinary tract obstruction necessitated surgical intervention[136].

ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE

Anti-glomerular basement membrane antibody (Anti-GBM) disease (Goodpasture's Syndrome) is a rare condition with an incidence of 1-2/million population/year. In this condition antibodies are generated against the alpha-3 chain of type IV collagen, found in the glomerular basement membrane. Haematuria in association with rapidly progressive glomerulonephritis and pulmonary haemorrhage are common features of this condition. No other urological manifestations of anti-GBM disease have been reported in the literature[147].

Cryoglobulinaemic vasculitis

Cryoglobulins are immunoglobulins that precipitate in the cold and dissolve on rewarming. There are three main types of cryoglobulins: (1) Type Ⅰ - a monoclonal antibody that is most commonly associated with lymphoma, Waldenström's macroglobulinemia, and multiple myeloma. Because type Ⅰ cryoglobulins do not easily activate complement, patients with type Ⅰ are usually asymptomatic until the level of cryoglobulinemia is sufficiently high to cause hyperviscosity syndrome; (2) Type Ⅱ - A mixture of both monoclonal and polyclonal cryoglobulins commonly associated with hepatitis C virus (HCV); and (3) Type Ⅲ-Rheumatoid factor is polyclonal in type Ⅲ and is usually associated with rheumatic disease and chronic infections especially HCV.

Type Ⅱ and Ⅲ cryoglobulinemia frequently presents as vasculitis, most commonly with recurrent lower extremity purpura, glomerulonephritis, and peripheral neuropathy. Glomerulonephritis with non-visible haematuria appears to be the only reported urological manifestation of Cryoglobulinaemic vasculitis[148,149].

Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)

Hypocomplementaemic urticarial Vasculitis (HUV) is a rare form of vasculitis characterised by urticarial lesions, biopsy evidence of small vessel vasculitis and hypocomplementaemia. There may also be other systemic findings including arthralgia or arthritis, mild glomerulonephritis, uveitis or episcleritis and recurrent abdominal pain. It is estimated that approximately 50% of all HUV patients will have renal involvement. Although this is usually mild, haematuria and proteinuria are commonly noted[150].

VARIABLE VESSEL VASCULITIS

Behçets disease

Behçets disease (BD) is a variable vessel vasculitis of unknown aetiology. BD is a multi-system chronic relapsing and remitting condition characterised by a triad of[151]: (1) Recurrent oral aphthous ulcers; (2) Genital ulcers; and (3) Uveitis.

Epidemiology: There is a peak incidence in the 3-5th decades of life. The exact aetiology and pathogenesis of BD remains unknown, although carriers of HLA B5/ HLA B51 are at increased risk of developing BD[152].

Clinical features and classification: Clinical manifestations of BD include recurrent aphthous ulcers of the oral mucosa, skin lesions, genital ulceration, ocular inflammatory lesions, arthritis, epididymitis, intestinal ulcers, vascular lesions, neuropsychiatric symptoms and a positive pathergy test (the forearm is pricked with a small, sterile needle-occurrence of a small red bump or pustule at the site of needle insertion constitutes a positive test). There is no one diagnostic test for BD and therefore diagnosis is usually clinical. A number of classifications have been published to aid in diagnosis including the "International Study Group Criteria", published in 1990, which is one of the most widely used and accepted (Table 3)[153].

Urological manifestations: A number of Urological manifestations of BD have been reported in the literature. The most common of these is genital ulceration. Genital ulceration in males is most commonly noted in the scrotal area but lesions may also be found on the shaft of the penis or in the peri-anal region. In women the labia are commonly affected, although vaginal and cervical ulcers can also occur[154]. Genital lesions are usually deeper and last longer than oral ulcers, they are also much more likely to cause significant scarring after they heal. A prospective study of 100 BD patients in Turkey (70 males and 30 females) reported genital ulceration in 89% of those enrolled[155]. In a separate survey of 2031 patients in Japan, genital lesions were present in 76% of the males and 83.8% of the females[156].

In a prospective study from Turkey of 100 BD patients, 6% of males had experienced episodes of epididymitis and a further 3% of males were found to have had episodes of sterile urethritis with discharge[155].

Bladder involvement is uncommon in BD and is mainly limited to vasculitis of the bladder wall and neuropathic bladder symptoms[157]. Direct involvement of blood vessels in the bladder wall may result in localised ischemia, which can progress, to mucosal necrosis and bladder ulceration, nodules or recurrent cystitis. This process is likely to be responsible for the haematuria, storage symptoms and urge incontinence that patients with bladder involvement in BD report[157]. There is also an isolated report of vesico-vaginal fistula as a result of posterior extension of the necrotic process in BD[158].

Approximately 5%-10% of BD patients have neurological disease involvement and of these patients approximately 5% report voiding symptoms[159]. Bladder symptoms secondary to neurological involvement in BD may vary considerably depending on the level of brain and spinal cord involvement. Detrusor areflexia, hyperreflexia and detrusor sphincter dysynergia have all been reported[160]. In severe cases there may be complete urinary retention, incontinence and hydronephrosis, necessitating surgical intervention. Augmentation ileocystoplasty in these patients has been shown to have good clinical outcomes[157]. Despite pathergy being a well-known phenomena in BD patients, cystoscopy, bladder biopsy, and even ileocystoplasty or radical cystoprostatectomy have been performed in this group without complication[157].

Management and prognosis: Management of patients with BD will depend largely on the specific organs affected by disease and the severity of organ involvement. In 2008 the European League Against Rheumatism (EULAR) published consensus guidelines on management of BD.

For mild oral and genital ulcerations, the current recommendation is for localised application of topical steroids or sucralfate solution, as a first-line therapy. Colchicine has been widely used in more severe cases of BD but the evidence suggests that additional benefit may only be gained in females with genital ulcers and patients with erythema nodosum[161,162]. For severe mucocutaneous lesions, systemic corticosteroids, azathioprine, interferon-alfa and TNF-alpha antagonists may be considered[163].

The management of bladder involvement in BD needs to be tailored to each individual bearing in mind their specific symptoms and findings on cystoscopy and urodynamic testing. This may include intermittent self-catheterisation for patients suffering from urinary retention and anti-cholinergics for patients suffering from urge incontinence or surgical intervention in more severe cases[164].

Cogan's syndrome

Cogan's syndrome (CS) is a rare variable vessel

Table 3 International Study Group Criteria for Behçets disease[153]

Required criteria	
Recurrent oral ulceration (obligatory)	Minor aphthous, major aphthous, or herpetiform ulceration (observed by physician or patient); recurring at least 3 times in a 12 mo period
Plus 2 of	
Recurrent genital ulceration	Aphthous ulceration or scarring (observed by physician or patient)
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum (observed by physician or patient), pseudofolliculitis, or papulopustular lesions; or acneiform nodules (observed by physician) in post-adolescent patients not on corticosteroid treatment
Positive Pathergy test	Read by physician at 24-48 h

vasculitis of young adults characterised by interstitial keratitis, vestibuloauditory dysfunction and other features including aortitis. There are no reported urogenital manifestations of CS[165].

TREATMENT RELATED UROLOGICAL ADVERSE EFFECTS

An important consideration for urologists is the use of potent immunosuppressive therapies for vasculitis and potential urological complications that may arise as a result of this.

The most well-known urological complication of immunosuppressive therapy is the association of cyclophosphamide with haemorrhagic cystitis and bladder cancer. The active metabolite of cyclophosphamide, acrolein, is excreted in urine and is toxic to urothelium. In a study of 145 GPA patients treated with daily oral cyclophosphamide in the United States, 73 patients (50%) experienced episodes of non-glomerular haematuria +/- dysuria. Sixty of these patients went on to have cystoscopic examination and cyclophosphamide-induced bladder injury was confirmed in 42 cases[166].

In the same study seven patients treated with oral cyclophosphamide for GPA subsequently developed transitional cell carcinoma of the bladder. All seven of these patients had previous episodes of non-glomerular haematuria and six of the patients had received a total cumulative cyclophosphamide dose exceeding 100 g, with the cumulative duration of cyclophosphamide therapy exceeding 2.7 years. On the basis of these findings the incidence of bladder cancer after the first exposure to cyclophosphamide was estimated at 5% at 10 years and 16% at 15 years. A series of 12 case reports of bladder cancer in association with cyclophosphamide, found that the disease phenotype in these patients was very aggressive, with all tumours grade 3 or 4 at the time of presentation[167].

Risk of developing bladder cancer appears to be related to cumulative dose and/or length of therapy received[168] Risk of cyclophosphamide associated bladder toxicity can be reduced *via* a number of measures: (1) Co-administration of sodium 2-mercaptoethanesulfonate (Mesna) inactivates acrolein in urine, protecting the bladder from its toxic effects. Some controversy exists with regards to the effectiveness of mesna therapy and at present "The American Society of Clinical Oncology" does not recommend the use of mesna in patients receiving cyclophosphamide except when high doses are used (*e.g.*, 50 mg/kg or 2 g/m^2). The EULAR however continue to recommend its use[169,170]; (2) Good hydration; (3) Treatment in the early morning to avoid overnight bladder accumulation of acrolein; and (4) Intermittent pulsed intravenous cyclophosphamide therapy rather than daily oral dosing. This has been shown to decrease the total cyclophosphamide dose received by up to half[171]. Consequently intermittent pulsed intravenous cyclophosphamide use is associated with a decreased incidence of drug-induced cystitis[172].

A bladder cancer surveillance program is also suggested for patients that have received cyclophosphamide therapy. It is recommended that urinalysis is obtained from these patients on a six monthly basis to screen for haematuria. This should be repeated within one week if haematuria is detected. Patients with confirmed non-glomerular haematuria should then undergo cystoscopy to exclude bladder cancer. For patients with cystoscopic evidence of bladder damage, the procedure should be repeated every 6 to 12 mo[166].

Cyclophosphamide is also teratogenic and causes gonadal toxicity. In females this may lead to irregularity of the menstrual cycle and reduced ovarian function. In males, alkylating drug therapy may reduce sperm count and testicular endocrine function[173]. A study of men with BD showed significant infertility after cyclophosphamide therapy with oligospermia or azoospermia occurring in 13 of 17 men treated with cyclophosphamide but in none of the 10 men treated with colchicine alone or in the four control patients who did not receive any treatment[174]. A separate study looking at the effect of colchicine alone on sperm production, in 62 male patients with BD, found evidence of oligonecrospermia in 37% of patients and azoospermia in 3% of patients[175].

Patients may have the option of cryopreservation of sperm and ova prior to commencing cyclophosphamide therapy. The induction of gonadal quiescence during

therapy with alkylating agents may minimize the risk of testicular and ovarian failure. Studies looking at the use of a gonadotropin-releasing hormone agonist such as leuprolide to achieve gonadal quiescence in women are ongoing and results remain inconclusive[176,177]. In male patients, studies are looking into adjuvant testosterone therapy to induce gonadal quiescence. Again the results remain inconclusive[178].

In both male and female patients where preservation of fertility is a consideration the patient's management should be discussed early on with local fertility services and consideration given to minimising or avoiding the use of alkylating agents.

CONCLUSION

The PSV are a heterogeneous group of rare disorders with many varying features and presentations, which may affect urological organs. PAN, HSP, BD and GPA are the PSV that have the most commonly reported urological manifestations. Testes, prostate and ureters are the most commonly involved urological organs. Identification of vasculitic disease in the urogenital tract is important as not only may this be the first presentation of systemic disease but also management with immunosuppressive therapy may allow rapid resolution of symptoms and avoid the need for invasive surgical management.

REFERENCES

1 **Jennette JC**, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**: 1-11 [PMID: 23045170 DOI: 10.1002/art.37715]

2 **Wen D**, Du X, Ma CS. Takayasu arteritis: diagnosis, treatment and prognosis. *Int Rev Immunol* 2012; **31**: 462-473 [PMID: 23215768 DOI: 10.3109/08830185.2012.740105]

3 **Alibaz-Oner F**, Aydin SZ, Direskeneli H. Advances in the diagnosis, assessment and outcome of Takayasu's arteritis. *Clin Rheumatol* 2013; **32**: 541-546 [PMID: 23271611 DOI: 10.1007/s10067-012-2149-3]

4 **Jghaimi F**, Kabbaj A, Essaadouni L. [Takayasu's arteritis and retroperitoneal fibrosis: a case report]. *Rev Med Interne* 2010; **31**: e1-e3 [PMID: 19231040 DOI: 10.1016/j.revmed.2009.01.001]

5 **Houman H**, Haouet S, Lamloum M, Ghorbel IB, Miled M. [Retroperitoneal fibrosis associated with Takayasu arteritis]. *Ann Med Interne* (Paris) 1998; **149**: 107-108 [PMID: 11490523]

6 **Fajac A**, Galezowski N, Cormier JM, Duclos FM, Herreman G. [Inflammatory arteritis of Takayasu's disease type and retroperitoneal fibrosis]. *Rev Med Interne* 1988; **9**: 436-437 [PMID: 2906167]

7 **Salvarani C**, Pipitone N, Versari A, Hunder GG. Clinical features of polymyalgia rheumatica and giant cell arteritis. *Nat Rev Rheumatol* 2012; **8**: 509-521 [PMID: 22825731 DOI: 10.1038/nrrheum.2012.97]

8 **Kermani TA**, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, Matteson EL. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis* 2013; **72**: 1989-1994 [PMID: 23253927 DOI: 10.1136/annrheumdis-2012-202408]

9 **Caylor TL**, Perkins A. Recognition and management of polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician* 2013; **88**: 676-684 [PMID: 24364483]

10 **Mackie SL**, Pease CT. Diagnosis and management of giant cell arteritis and polymyalgia rheumatica: challenges, controversies and practical tips. *Postgrad Med J* 2013; **89**: 284-292 [PMID: 23355687 DOI: 10.1136/postgradmedj-2012-131400]

11 **Gonzalez-Gay MA,** Garcia-Porrua C, Llorca J, Hajeer AH, Branas F, Dababneh A, Gonzalez-Louzao C, Rodriguez-Gil E, Rodriguez-Ledo P, Ollier WE. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine* 2000; **79**: 283-292 [PMID 11039076]

12 **Arnillas E**, de la Fuente J, Núñez M, Domínguez F. [Giant cell arteritis with epididymal involvement]. *Med Clin* (Barc) 2009; **132**: 485 [PMID: 19344797 DOI: 10.1016/j.medcli.2008.07.020]

13 **Sundaram S**, Smith DH. Giant cell arteritis mimicking a testicular tumour. *Rheumatol Int* 2001; **20**: 215-216 [PMID: 11518043]

14 **Ronco P**, Verroust P, Mignon F, Kourilsky O, Vanhille P, Meyrier A, Mery JP, Morel-Maroger L. Immunopathological studies of polyarteritis nodosa and Wegener's granulomatosis: a report of 43 patients with 51 renal biopsies. *Q J Med* 1983; **52**: 212-223 [PMID: 6193553]

15 **Somer T**, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; **20**: 1010-1036 [PMID: 7795045]

16 **Hughes LB**, Bridges SL. Polyarteritis nodosa and microscopic polyangiitis: etiologic and diagnostic considerations. *Curr Rheumatol Rep* 2002; **4**: 75-82 [PMID: 11798986 DOI: 10.1007/s11926-002-0027-8]

17 **Watts RA**, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000; **43**: 414-419 [PMID: 10693883 DOI: 10.1002/1529-0131(200002)43: 2<414: : aid-anr23>3.0.co; 2-0]

18 **Stone JH**. Polyarteritis nodosa. *JAMA* 2002; **288**: 1632-1639 [PMID: 12350194 DOI: 10.1001/jama.288.13.1632]

19 **González-Gay MA**, García-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine* (Baltimore) 1999; **78**: 292-308 [PMID: 10499071]

20 **Mahr A**, Guillevin L, Poissonnet M, Aymé 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**: 92-99 [PMID: 14872461 DOI: 10.1093/rheumatology/kem107]

21 **Pagnoux C**, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, Bienvenu B, Mouthon L, Guillevin L. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 2010; **62**: 616-626 [PMID: 20112401 DOI: 10.1002/art.27240]

22 **Guillevin L,** Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, Noël L-H, Trépo C. Polyarteritis nodosa related to hepatitis b virus a prospective study with long-term observation of 41 patients. *Medicine* 1995; **74:** 238-253 [PMID: 7565065]

23 **Trepo C**, Guillevin L. Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis. *J Autoimmun* 2001; **16**: 269-274 [PMID: 11334492 DOI: 10.1006/jaut.2000.0502]

24 **Jee KN**, Ha HK, Lee IJ, Kim JK, Sung KB, Cho KS, Kim PN, Lee MG, Lim HK, Choi CS, Auh YH. Radiologic findings of abdominal polyarteritis nodosa. *AJR Am J Roentgenol* 2000; **174**: 1675-1679 [PMID: 10845504 DOI: 10.2214/ajr.174.6.1741675]

25 **Croker BP**, Lee T, Gunnells JC. Clinical and pathologic features of polyarteritis nodosa and its renal-limited variant: primary crescentic and necrotizing glomerulonephritis. *Hum Pathol* 1987; **18**: 38-44 [PMID: 2880791 DOI: 10.1016/S0046-8177(87)80191-0]

26 **Wees SJ**, Sunwoo IN, Oh SJ. Sural nerve biopsy in systemic necrotizing vasculitis. *Am J Med* 1981; **71**: 525-532 [PMID: 6116431 DOI: 10.1016/0002-9343(81)90195-9]

27 **Albert DA**, Rimon D, Silverstein MD. The diagnosis of polyarteritis nodosa. I. A literature-based decision analysis approach. *Arthritis Rheum* 1988; **31**: 1117-1127 [PMID: 2901840 DOI: 10.1002/art.1780310906]

28 **Lightfoot RW**, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, Arend WP, Calabrese LH, Leavitt RY, Lie JT. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; **33**: 1088-1093 [PMID: 1975174 DOI: 10.1002/art.1780330805]

29 **Guillevin L**, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996; **75**: 17-28 [PMID: 8569467]

30 **Ribi C**, Cohen P, Pagnoux C, Mahr A, Arène JP, Puéchal X, Carli P, Kyndt X, Le Hello C, Letellier P, Cordier JF, Guillevin L. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. *Arthritis Rheum* 2010; **62**: 1186-1197 [PMID: 20131268 DOI: 10.1002/art.27340]

31 **Guillevin L**, Cohen P, Mahr A, Arène JP, Mouthon L, Puéchal X, Pertuiset E, Gilson B, Hamidou M, Lanoux P, Bruet A, Ruivard M, Vanhille P, Cordier JF. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003; **49**: 93-100 [PMID: 12579599 DOI: 10.1002/art.10922]

32 **Guillevin L**, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, Pourrat J, Christoforov B, Trépo C. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. *Ann Rheum Dis* 1994; **53**: 334-337 [PMID: 7912504 DOI: 10.1136/ard.53.5.334]

33 **Guillevin L**, Mahr A, Cohen P, Larroche C, Queyrel V, Loustaud-Ratti V, Imbert B, Hausfater P, Roudier J, Bielefeld P, Petitjean P, Smadja D. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum* 2004; **51**: 482-487 [PMID: 15188337 DOI: 10.1002/art.20401]

34 **Azar N**, Guillevin L, Huong Du LT, Herreman G, Meyrier A, Godeau P. Symptomatic urogenital manifestations of polyarteritis nodosa and Churg-Strauss angiitis: analysis of 8 of 165 patients. *J Urol* 1989; **142**: 136-138 [PMID: 2567358]

35 **Teichman JM**, Mattrey RF, Demby AM, Schmidt JD. Polyarteritis nodosa presenting as acute orchitis: a case report and review of the literature. *J Urol* 1993; **149**: 1139-1140 [PMID: 8097793]

36 **Toepfer NJ**, Lountzis NI, Ugoeke JC, Ferringer TC. Polyarteritis nodosa with bilateral asynchronous testicular necrosis: a case report. *Case Rep Urol* 2011; **2011**: 465353 [PMID: 22606613 DOI: 10.1155/2011/465353]

37 **Pannek J**, Haupt G. Orchitis due to vasculitis in autoimmune diseases. *Scand J Rheumatol* 1997; **26**: 151-154 [PMID: 9225868]

38 **Warfield AT**, Lee SJ, Phillips SM, Pall AA. Isolated testicular vasculitis mimicking a testicular neoplasm. *J Clin Pathol* 1994; **47**: 1121-1123 [PMID: 7876390]

39 **Atis G**, Memis OF, Güngör HS, Arikan O, Saglican Y, Caskurlu T. Testicular polyarteritis nodosa mimicking testicular neoplasm. *ScientificWorldJournal* 2010; **10**: 1915-1918 [PMID: 20890580 DOI: 10.1100/tsw.2010.194]

40 **Dotan ZA**, Laufer M, Heldenberg E, Langevitz P, Fridman E, Duvdevani M, Ramon J. Isolated testicular polyarteritis nodosa mimicking testicular neoplasm-long-term follow-up. *Urology* 2003; **62**: 352 [PMID: 12893362]

41 **Fraenkel-Rubin M**, Ergas D, Sthoeger ZM. Limited polyarteritis nodosa of the male and female reproductive systems: diagnostic and therapeutic approach. *Ann Rheum Dis* 2002; **61**: 362-364 [PMID: 11874844 DOI: 10.1136/ard.61.4.362]

42 **Kolar P**, Schneider U, Filimonow S, Burmester GR, Buttgereit F. Polyarteritis nodosa and testicular pain: ultrasonography reveals vasculitis of the testicular artery. *Rheumatology* (Oxford) 2007; **46**: 1377-1378 [PMID: 17586861 DOI: 10.1093/rheumatology/kem165]

43 **Meeuwissen J**, Maertens J, Verbeken E, Blockmans D. Case reports: testicular pain as a manifestation of polyarteritis nodosa. *Clin Rheumatol* 2008; **27**: 1463-1466 [PMID: 18651100 DOI: 10.1007/s10067-008-0970-5]

44 **Susanto CR**, Fedder G, Looijen-Salamon MG. Acute, painful, and swollen testicle as the presenting feature in polyarteritis nodosa. *Eur J Intern Med* 2003; **14**: 441-443 [PMID: 14614979]

45 **Tanuma Y**, Oda T, Yokoo A, Ito S, Takeuchi K. Recurrent polyarteritis nodosa limited to the testis. *J Urol* 2003; **170**: 1953 [PMID: 14532825 DOI: 10.1097/01.ju.0000089740.11360.e0]

46 **Brimo F**, Lachapelle J, Epstein JI. Testicular vasculitis: a series of 19 cases. *Urology* 2011; **77**: 1043-1048 [PMID: 21419476 DOI: 10.1016/j.urology.2011.01.021]

47 **Abós Fanlo P**, Vilardell Tarrés M, Pastor Mouron J, Solé-Balcells F, Tornos Solano J. Secondary hydronephrosis to polyarteritis nodosa. *Eur Urol* 1979; **5**: 211-213 [PMID: 36277]

48 **Bulbuloglu E**, Kantarceken B, Yuksel M, Ciralik H, Sahinkanat T, Kale IT. An unusual presentation of polyarteritis nodosa: A case report. *West Indian Med J* 2006; **55**: 56-59 [PMID: 16755822]

49 **Duclos JM**, Bensadoun H, Herreman G, Baviera E. [Pseudotumor of the ureter manifesting periarteritis nodosa]. *Ann Urol* (Paris) 1984; **18**: 418-419 [PMID: 6152385]

50 **Ekeland A**, Sander S. Stenosis of the ureter caused by periarteritis. *J Oslo City Hosp* 1974; **24**: 78-82 [PMID: 4153076]

51 **Glanz I**, Grünebaum M. Ureteral changes in polyarteritis nodosa as seen during excretory urography. *J Urol* 1976; **116**: 731-733 [PMID: 12376]

52 **Hefty TR**, Bonafede P, Stenzel P. Bilateral ureteral stricture from polyarteritis nodosa. *J Urol* 1989; **141**: 600-601 [PMID: 2563780]

53 **Kaskarelis IS**, Zarifi M, Dantis P, Vrachliotis G. Bilateral ureteral involvement in polyarteritis nodosa. *Scand J Urol Nephrol* 1995; **29**: 323-326 [PMID: 8578276]

54 **Melin JP**, Lemaire P, Birembaut P, Aubert L, Cohen J, Lardennois B, Chanard J. Polyarteritis nodosa with bilateral ureteric involvement. *Nephron* 1982; **32**: 87-89 [PMID: 6129579]

55 **Samellas W**, Bellonias E, Papacharalampous N. Polyarteritis nodosa: ureteral involvement. *J Urol* 1971; **105**: 186-187 [PMID: 4397427]

56 **Casserly LF**, Reddy SM, Rennke HG, Carpinito GA, Levine JS. Reversible bilateral hydronephrosis without obstruction in hepatitis B-associated polyarteritis nodosa. *Am J Kidney Dis* 1999; **34**: e11 [PMID: 10471757]

57 **Zhang JQ**, Fielding JR, Zou KH. Etiology of spontaneous perirenal hemorrhage: a meta-analysis. *J Urol* 2002; **167**: 1593-1596 [PMID: 11912370 DOI: 10.1016/S0022-5347(05)65160-9]

58 **Koc O**, Ozbek O, Gumus S, Demir A. Endovascular management of massive gastrointestinal bleeding associated with polyarteritis nodosa. *J Vasc Interv Radiol* 2009; **20**: 277-279 [PMID: 19054689 DOI: 10.1016/j.jvir.2008.10.023]

59 **Burns JC**, Glodé MP. Kawasaki syndrome. *Lancet* 2004; **364**: 533-544 [PMID: 15302199 DOI: 10.1016/s0140-6736(04)16814-1]

60 **Freeman AF**, Shulman ST. Kawasaki disease: summary of the American Heart Association guidelines. *Am Fam Physician* 2006; **74**: 1141-1148 [PMID: 17039750]

61 **Subramaniam R**, Lama T, Chong CY. Pelviureteric junction obstruction as sequelae of Kawasaki disease. *Pediatr Surg Int* 2004; **20**: 553-555 [PMID: 15248077 DOI: 10.1007/s00383-004-1218-3]

62 **Connolly KD**, Timmons D. Mucocutaneous lymph node syndrome with testicular involvement. *Ir J Med Sci* 1980; **149**: 26-27 [PMID: 7380632]

63 **Newburger JW**, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, Colan SD, Duffy CE, Fulton DR, Glode MP. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; **324**: 1633-1639 [PMID: 1709446 DOI: 10.1056/nejm199106063242305]

64 **Harper L**, Savage CO. ANCA-associated renal vasculitis at the end

of the twentieth century--a disease of older patients. *Rheumatology* (Oxford) 2005; **44**: 495-501 [PMID: 15613403 DOI: 10.1093/rheumatology/keh522]

65 **Hoffman GS**, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116**: 488-498 [PMID: 1739240]

66 **Guillevin L**, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, Amouroux J, Casassus P, Jarrousse B. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999; **42**: 421-430 [PMID: 10088763 DOI: 10.1002/1529-0131(199904)42: 3<421: : AID-ANR5>3.0.CO; 2-6]

67 **Guillevin L**, Le Thi Huong Du, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. *Br J Rheumatol* 1988; **27**: 258-264 [PMID: 2900659]

68 **Schönermarck U**, Lamprecht P, Csernok E, Gross WL. Prevalence and spectrum of rheumatic diseases associated with proteinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA. *Rheumatology* (Oxford) 2001; **40**: 178-184 [PMID: 11257154]

69 **Bhamra K**, Luqmani R. Damage assessment in ANCA-associated vasculitis. *Curr Rheumatol Rep* 2012; **14**: 494-500 [PMID: 22983618 DOI: 10.1007/s11926-012-0291-1]

70 **Li X**, Chen N. Management of crescentic glomerulonephritis: what are the recent advances? *Contrib Nephrol* 2013; **181**: 229-239 [PMID: 23689584 DOI: 10.1159/000348479]

71 **Talarico R**, Baldini C, Della Rossa A, Carli L, Tani C, Bombardieri S. Systemic vasculitis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2013; **31**: S84-S88 [PMID: 23663686]

72 **Rich EN**, Brown KK. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis. *Curr Opin Pulm Med* 2012; **18**: 447-454 [PMID: 22854508 DOI: 10.1097/MCP.0b013e32835701d6]

73 **Heldmann F**, Brandt J, Schoppe H, Braun J. [A 46-year-old-patient with granulomatous prostatitis, arthralgia and haemorrhagic rhinitis]. *Dtsch Med Wochenschr* 2006; **131**: 22-25 [PMID: 16374738 DOI: 10.1055/s-2006-924915]

74 **Menown IB**, McKane WR, Kennedy JA, Kelly IM, Maclennan BA, Best BG, Walsh MY. Detection and follow-up of Wegener's prostatitis by transrectal ultrasound. *Br J Rheumatol* 1998; **37**: 805-806 [PMID: 9714370]

75 **Mundinger A**, Pumpe K, Grosser G, Herbst EW, Grotz W, Kröpelin T. [Primary manifestation of Wegener's granulomatosis of the prostate]. *Urologe A* 1989; **28**: 234-236 [PMID: 2474881]

76 **Stillwell TJ**, DeRemee RA, McDonald TJ, Weiland LH, Engen DE. Prostatic involvement in Wegener's granulomatosis. *J Urol* 1987; **138**: 1251-1253 [PMID: 2444721]

77 **Pumpe K**, Mundinger A, Herbst EW, Peter P. [An unusual course of Wegener's granulomatosis: initial manifestation in the prostate and development of arterial microaneurysms in the kidney]. *Pathologe* 1989; **10**: 318-321 [PMID: 2798359]

78 **Huong DL**, Papo T, Piette JC, Wechsler B, Bletry O, Richard F, Valcke JC, Godeau P. Urogenital manifestations of Wegener granulomatosis. *Medicine* (Baltimore) 1995; **74**: 152-161 [PMID: 7760722]

79 **Vaught WW**, Wilson TM, Raife MJ, Horne DW. Wegener granulomatosis: prostatic involvement and bladder outlet obstruction. *Urology* 1989; **34**: 43-45 [PMID: 2749956]

80 **Gaber KA**, Ryley NG, Macdermott JP, Goldman JM. Wegener's granulomatosis involving prostate. *Urology* 2005; **66**: 195 [PMID: 16014287 DOI: 10.1016/j.urology.2005.01.045]

81 **Gunnarsson R**, Omdal R, Kjellevold KH, Ellingsen CL. Wegener's granulomatosis of the prostate gland. *Rheumatol Int* 2004; **24**: 120-122 [PMID: 12879271 DOI: 10.1007/s00296-003-0343-y]

82 **Middleton G**, Karp D, Lee E, Cush J. Wegener's granulomatosis presenting as lower back pain with prostatitis and ureteral obstruction. *J Rheumatol* 1994; **21**: 566-569 [PMID: 8006905]

83 **Davies CW**, Wathen CG. Wegener's granulomatosis presenting as prostate and submandibular gland disease. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; **14**: 190-191 [PMID: 9306514]

84 **Murty GE**, Powell PH. Wegener's granulomatosis presenting as prostatitis. *Br J Urol* 1991; **67**: 107-108 [PMID: 1993268]

85 **Brunner A**, Tzankov A, Akkad T, Lhotta K, Bartsch G, Mikuz G. Wegener's granulomatosis presenting with gross hematuria due to prostatitis. *Virchows Arch* 2004; **444**: 92-94 [PMID: 14576940 DOI: 10.1007/s00428-003-0916-x]

86 **Sözer IT**. Wegener's granulomatosis with infiltration of the prostate. *Br J Urol* 1986; **58**: 335 [PMID: 3719257]

87 **Yalowitz PA**, Greene LF, Sheps SG, Carlin MR. Wegener's granulomatosis involving the prostate gland: report of a case. *J Urol* 1966; **96**: 801-804 [PMID: 5923308]

88 **Minnee RC**, van den Berk GE, Groeneveld JO, van Dijk J, Turkcan K, Visser MJ, Vahl AC. Aortic aneurysm and orchitis due to Wegener's granulomatosis. *Ann Vasc Surg* 2009; **23**: 786.e15-786.e19 [PMID: 19748223 DOI: 10.1016/j.avsg.2009.06.011]

89 **Paik ML**, MacLennan GT, Seftel AD. Embolic testicular infarction secondary to nonbacterial thrombotic endocarditis in Wegener's granulomatosis. *J Urol* 1999; **161**: 919-920 [PMID: 10022717]

90 **Lee SS**, Tang SH, Sun GH, Yu CP, Jin JS, Chang SY. Limited Wegener's granulomatosis of the epididymis and testis. *Asian J Androl* 2006; **8**: 737-739 [PMID: 16855769 DOI: 10.1111/j.1745-7262.2006.00207.x]

91 **Barber TD**, Al-Omar O, Poulik J, McLorie GA. Testicular infarction in a 12-year-old boy with Wegener's granulomatosis. *Urology* 2006; **67**: 846.e9-846.10 [PMID: 16566986 DOI: 10.1016/j.urology.2005.10.036]

92 **Hernández-Rodríguez J**, Tan CD, Koening CL, Khasnis A, Rodríguez ER, Hoffman GS. Testicular vasculitis: findings differentiating isolated disease from systemic disease in 72 patients. *Medicine* (Baltimore) 2012; **91**: 75-85 [PMID: 22391469 DOI: 10.1097/MD.0b013e31824156a7]

93 **Davenport A**, Downey SE, Goel S, Maciver AG. Wegener's granulomatosis involving the urogenital tract. *Br J Urol* 1996; **78**: 354-357 [PMID: 8881941]

94 **Di Comite G**, Bonavida G, Bozzolo E, Bianchi S, Ciboddo G, Tresoldi M, Praderio L, Sabbadini MG. [Wegener's granulomatosis: an analysis of 50 patients]. *Reumatismo* 2005; **57**: 187-192 [PMID: 16258603]

95 **Guillevin L**, Brauner M. Magnetic resonance imaging of ureter stenosis in Wegener's granulomatosis. *Ann Med Interne* (Paris) 1998; **149**: 287 [PMID: 9791562]

96 **Rich LM**, Piering WF. Ureteral stenosis due to recurrent Wegener's granulomatosis after kidney transplantation. *J Am Soc Nephrol* 1994; **4**: 1516-1521 [PMID: 8025224]

97 **Sataa S**, Ben Rhouma S, Tanguour M, Rebai S, Cherif K, Kchir N, Nouira Y, Benrais N, Horchani A. Ureteral stenosis due to Wegener's granulomatosis. *Tunis Med* 2011; **89**: 725-726 [PMID: 21948672]

98 **Ben Ghorbel I**, Chebbi W, Zouari M, Hentati F, Miled M, Houman MH. [Ureteral stenosis in Wegener's granulomatosis. Case report]. *Presse Med* 2006; **35**: 1659-1663 [PMID: 17086121]

99 **Matsuda S**, Mitsukawa S, Ishii N, Shirai M. A case of Wegener's granulomatosis with necrosis of the penis. *Tohoku J Exp Med* 1976; **118**: 145-151 [PMID: 982429]

100 **Stucker F**, Masouyé I, Toutous-Trellu L. Fever and penis ulcer in an 87-year-old man. *Dermatology* 2006; **212**: 397-398 [PMID: 16707897 DOI: 10.1159/000092298]

101 **Bories N**, Becuwe C, Marcilly MC, Wolf F, Balme B, Thomas L. Glans penis ulceration revealing Wegener's granulomatosis. *Dermatology* 2007; **214**: 187-189 [PMID: 17341873 DOI: 10.1159/000098583]

102 **Ebo DG**, Mertens AV, De Clerck LS, Gentens P, Daelemans R. Relapse of Wegener's granulomatosis presenting as a destructive urethritis and penile ulceration. *Clin Rheumatol* 1998; **17**: 239-241 [PMID: 9694061 DOI: 10.1007/BF01451056]

103 **Palacios J**, Picazo ML, Enríquez R, de Miguel JL. [Unusual clinical manifestations in a case of Wegener's disease]. *Med Clin* (Barc) 1986; **87**: 870 [PMID: 3492641]

104 **Dufour JF**, Le Gallou T, Cordier JF, Aumaître O, Pinède L, Aslangul E, Pagnoux C, Marie I, Puéchal X, Decaux O, Dubois A, Agard C, Mahr A, Comoz F, Boutemy J, Broussolle C, Guillevin L, Sève P, Bienvenu B. Urogenital manifestations in Wegener

granulomatosis: a study of 11 cases and review of the literature. *Medicine* (Baltimore) 2012; **91**: 67-74 [PMID: 22391468 DOI: 10.1097/MD.0b013e318239add6]
105 **Jensen KM**, Nielsen KK, Kock K. Necrotising urethritis in Wegener's granulomatosis. *Br J Urol* 1982; **54**: 435-436 [PMID: 7116115]
106 **Fowler M**, Martin SA, Bowles WT, Packman R, Katzenstein AL. Wegener granulomatosis. Unusual cause of necrotizing urethritis. *Urology* 1979; **14**: 66-69 [PMID: 452226]
107 **Verswijvel G**, Eerens I, Messiaen T, Oyen R. Granulomatous renal pseudotumor in Wegener's granulomatosis: imaging findings in one case. *Eur Radiol* 2000; **10**: 1265-1267 [PMID: 10939487]
108 **Hooda D**, Parsons J, Hooda S, Nuss M, Layne R. Isolated bladder vasculitis: a rare presentation of Wegener's granulomatosis. *W V Med J* 2011; **107**: 24-25 [PMID: 21322469]
109 **Ashikaga E**, Iyoda M, Suzuki H, Nagai H, Shibata T, Akizawa T. [Case of microscopic polyangiitis presenting initially as prostatic vasculitis]. *Nihon Jinzo Gakkai Shi* 2009; **51**: 1075-1079 [PMID: 19999587]
110 **Lamarche JA**, Peguero AM, Rosario JO, Patel A, Courville C. Anti-MPO small-vessel vasculitis causing prostatis and nephritis. *Clin Exp Nephrol* 2007; **11**: 180-183 [PMID: 17593520 DOI: 10.1007/s10157-007-0473-8]
111 **Kiyokawa H**, Koyama M, Kato H. Churg-Strauss syndrome presenting with eosinophilic prostatitis. *Int J Urol* 2006; **13**: 838-840 [PMID: 16834677 DOI: 10.1111/j.1442-2042.2006.01419.x]
112 **Symes A**, Kalsi V, Rickards D, Allen C, Choong S, Philp T. Dystrophic ureteral calcification associated with Churg-Strauss vasculitis. *Urology* 2004; **64**: 1231.e9-1231.11 [PMID: 15596209 DOI: 10.1016/j.urology.2004.06.036]
113 **Walsh I**, Loughridge WG, Keane PF. Eosinophilic vasculitis (Churg-Strauss syndrome) involving the urethra. *Br J Urol* 1994; **74**: 255-256 [PMID: 7921951 DOI: 10.1111/j.1464-410X.1994.tb16601.x]
114 **Dolezalová P**, Telekesová P, Nemcová D, Hoza J. Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. *J Rheumatol* 2004; **31**: 2295-2299 [PMID: 15517648]
115 **Gardner-Medwin JM**, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; **360**: 1197-1202 [PMID: 12401245 DOI: 10.1016/S0140-6736(02)11279-7120]
116 **Yang YH**, Hung CF, Hsu CR, Wang LC, Chuang YH, Lin YT, Chiang BL. A nationwide survey on epidemiological characteristics of childhood Henoch-Schönlein purpura in Taiwan. *Rheumatology* (Oxford) 2005; **44**: 618-622 [PMID: 15671050 DOI: 10.1093/rheumatology/keh544]
117 **Blanco R**, Martínez-Taboada VM, Rodríguez-Valverde V, García-Fuentes M, González-Gay MA. Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997; **40**: 859-864 [PMID: 9153547 DOI: 10.1002/art.1780400513]
118 **Pillebout E**, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schönlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; **13**: 1271-1278 [PMID: 11961015]
119 **Rostoker G**. Schönlein-henoch purpura in children and adults: diagnosis, pathophysiology and management. *BioDrugs* 2001; **15**: 99-138 [PMID: 11437679 DOI: 10.2165/00063030-200115020-00004]
120 **Saulsbury FT**. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine* (Baltimore) 1999; **78**: 395-409 [PMID: 10575422]
121 **Dillon MJ**. Henoch-Schönlein purpura (treatment and outcome). *Cleve Clin J Med* 2002; **69** Suppl 2: SII121-SII123 [PMID: 12086251 DOI: 10.3949/ccjm.69.Suppl_2.SII12]
122 **Trapani S**, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, De Martino M. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005; **35**: 143-153 [PMID: 16325655 DOI: 10.1016/j.semarthrit.2005.08.007]
123 **Pfister C**, Liard-Zmuda A, Dacher J, Dubois D, Grise P, Mitrofanoff P. Total bilateral ureteral replacement for stenosing ureteritis in Henoch-Schönlein purpura. *Eur Urol* 2000; **38**: 96-99 [PMID: 10859449]
124 **Macpherson RI**. The radiological manifestations of Henoch-Schoenlein purpura. *J Can Assoc Radiol* 1974; **25**: 275-281 [PMID: 4443362]
125 **Pery M**, Alon U, Lachter JH, Kaftori JK, Gaitini D, Rosenberger A. The value of ultrasound in Schoenlein-Henoch purpura. *Eur J Pediatr* 1990; **150**: 92-94 [PMID: 2279515 DOI: 10.1007/BF02072045]
126 **Sandell J**, Ramanan R, Shah D. Penile involvement in Henoch-Schonlein purpura. *Indian J Pediatr* 2002; **69**: 529-530 [PMID: 12139142 DOI: 10.1007/BF02722659]
127 **Ferrara P**, Marrone G, Nicoletti A, Mastrangelo A, Tiberi E, Rigante D, Stabile A. Penile involvement in Henoch-Schönlein purpura with good prognosis. *Scand J Urol Nephrol* 2007; **41**: 567-569 [PMID: 17853026 DOI: 10.1080/00365590701365487]
128 **Clark WR**, Kramer SA. Henoch-Schönlein purpura and the acute scrotum. *J Pediatr Surg* 1986; **21**: 991-992 [PMID: 3794962 DOI: 10.1016/S0022-3468(86)80120-8]
129 **Katz S**, Borst M, Seekri I, Grosfeld JL. Surgical evaluation of Henoch-Schönlein purpura. Experience with 110 children. *Arch Surg* 1991; **126**: 849-853; discussion 853-854 [PMID: 1854244 DOI: 10.1001/archsurg.1991.01410310059008]
130 **Ben-Sira L**, Laor T. Severe scrotal pain in boys with Henoch-Schönlein purpura: incidence and sonography. *Pediatr Radiol* 2000; **30**: 125-128 [PMID: 10663526 DOI: 10.1007/s002470050029]
131 **Chamberlain RS**, Greenberg LW. Scrotal involvement in Henoch-Schönlein purpura: a case report and review of the literature. *Pediatr Emerg Care* 1992; **8**: 213-215 [PMID: 1513732]
132 **Mintzer CO**, Nussinovitch M, Danziger Y, Mimouni M, Varsano I. Scrotal involvement in Henoch-Schönlein purpura in children. *Scand J Urol Nephrol* 1998; **32**: 138-139 [PMID: 9606788 DOI: 10.1080/003655998750014530]
133 **Khan AU**, Williams TH, Malek RS. Acute scrotal swelling in Henoch-Schönlein syndrome. *Urology* 1977; **10**: 139-141 [PMID: 898453]
134 **Lind J**, Mackay A, Withers SJ. Henoch-Schönlein purpura and priapism. *J Paediatr Child Health* 2002; **38**: 526-527 [PMID: 12354274]
135 **Diana A**, Gaze H, Laubscher B, De Meuron G, Tschantz P. A case of pediatric Henoch-Schönlein purpura and thrombosis of spermatic veins. *J Pediatr Surg* 2000; **35**: 1843 [PMID: 11101753 DOI: 10.1053/jpsu.2000.9293]
136 **Søreide K**. Surgical management of nonrenal genitourinary manifestations in children with Henoch-Schönlein purpura. *J Pediatr Surg* 2005; **40**: 1243-1247 [PMID: 16080926 DOI: 10.1016/j.jpedsurg.2005.05.005]
137 **Loh HS**, Jalan OM. Testicular torsion in Henoch--Schonlein syndrome. *Br Med J* 1974; **2**: 96-97 [PMID: 4545143]
138 **Connolly B**, O'Halpin D. Sonographic evaluation of the abdomen in Henoch-Schonlein purpura. *Clin Radiol* 1994; **49**: 320-323 [PMID: 8013195 DOI: 10.1016/S0009-9260(05)81796-9]
139 **Ronkainen J**, Koskimies O, Ala-Houhala M, Antikainen M, Merenmies J, Rajantie J, Ormälä T, Turtinen J, Nuutinen M. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2006; **149**: 241-247 [PMID: 16887443 DOI: 10.1016/j.jpeds.2006.03.024]
140 **Chartapisak W**, Opastiraku S, Willis NS, Craig JC, Hodson EM. Prevention and treatment of renal disease in Henoch-Schönlein purpura: a systematic review. *Arch Dis Child* 2009; **94**: 132-137 [PMID: 18701559 DOI: 10.1136/adc.2008.141820]
141 **Saulsbury FT**. Clinical update: Henoch-Schönlein purpura. *Lancet* 2007; **369**: 976-978 [PMID: 17382810 DOI: 10.1016/S0140-6736(07)60474-7]
142 **Huber AM**, King J, McLaine P, Klassen T, Pothos M. A randomized, placebo-controlled trial of prednisone in early Henoch Schönlein Purpura [ISRCTN85109383]. *BMC Med* 2004; **2**: 7

[PMID: 15059282 DOI: 10.1186/1741-7015-2-7]
143 **Donnithorne KJ**, Atkinson TP, Hinze CH, Nogueira JB, Saeed SA, Askenazi DJ, Beukelman T, Cron RQ. Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. *J Pediatr* 2009; **155**: 136-139 [PMID: 19559299 DOI: 10.1016/j.jpeds.2008.12.049]
144 **Jauhola O**, Ronkainen J, Autio-Harmainen H, Koskimies O, Ala-Houhala M, Arikoski P, Hölttä T, Jahnukainen T, Rajantie J, Ormälä T, Nuutinen M. Cyclosporine A vs. methylprednisolone for Henoch-Schönlein nephritis: a randomized trial. *Pediatr Nephrol* 2011; **26**: 2159-2166 [PMID: 21626222 DOI: 10.1007/s00467-011-1919-5]
145 **Flynn JT**, Smoyer WE, Bunchman TE, Kershaw DB, Sedman AB. Treatment of Henoch-Schönlein Purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001; **21**: 128-133 [PMID: 11359020 DOI: 10.1159/000046235]
146 **Gedalia A**. Henoch-Schönlein purpura. *Curr Rheumatol Rep* 2004; **6**: 195-202 [PMID: 15134598 DOI: 10.1007/s11926-004-0068-2]
147 **Kambham N**. Crescentic Glomerulonephritis: an update on Pauci-immune and Anti-GBM diseases. *Adv Anat Pathol* 2012; **19**: 111-124 [PMID: 22313839 DOI: 10.1097/PAP.0b013e318248b7a1]
148 **Schena FP**. Survey of the Italian Registry of Renal Biopsies. Frequency of the renal diseases for 7 consecutive years. The Italian Group of Renal Immunopathology. *Nephrol Dial Transplant* 1997; **12**: 418-426 [PMID: 9075118 DOI: 10.1093/ndt/12.3.418]
149 **Braun GS**, Horster S, Wagner KS, Ihrler S, Schmid H. Cryoglobulinaemic vasculitis: classification and clinical and therapeutic aspects. *Postgrad Med J* 2007; **83**: 87-94 [PMID: 17308210 DOI: 10.1136/pgmj.2006.046078]
150 **Buck A**, Christensen J, McCarty M. Hypocomplementemic urticarial vasculitis syndrome: a case report and literature review. *J Clin Aesthet Dermatol* 2012; **5**: 36-46 [PMID: 22328958]
151 Behçet's disease. *Lancet* 1989; **1**: 761-762 [PMID: 2564568 DOI: 10.1016/S0140-6736(89)92578-6]
152 **Khairallah M**, Accorinti M, Muccioli C, Kahloun R, Kempen JH. Epidemiology of Behçet disease. *Ocul Immunol Inflamm* 2012; **20**: 324-335 [PMID: 23030353 DOI: 10.3109/09273948.2012.723112]
153 Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; **335**: 1078-1080 [PMID: 1970380 DOI: 10.1016/0140-6736(90)92643-V]
154 **Yazici H,** Fresko I, Hamuryudan V, Mat C, Melikoglu M, Ozyazgan Y, Tuzun Y, Yurdakul S. Behçet's syndrome. In: Mallia C, Uitto J Rheumaderm. USA: Springer, 1999: 135-140 [DOI: 10.1007/978-1-4615-4857-7_19]
155 **Kirkali Z**, Yigitbasi O, Sasmaz R. Urological aspects of Behçet's disease. *Br J Urol* 1991; **67**: 638-639 [PMID: 2070210 DOI: 10.1111/j.1464-410X.1991.tb15230.x]
156 **Mishima S**, Masuda K, Izawa Y, Mochizuki M, Namba K. The eighth Frederick H. Verhoeff Lecture. presented by saiichi mishima, MD Behçet's disease in Japan: ophthalmologic aspects. *Trans Am Ophthalmol Soc* 1979; **77**: 225-279 [PMID: 397657]
157 **Cetinel B**, Akpinar H, Tüfek I, Uygun N, Solok V, Yazici H. Bladder involvement in Behçet's syndrome. *J Urol* 1999; **161**: 52-56 [PMID: 10037367 DOI: 10.1016/S0022-5347(01)62060-3]
158 **Monteiro H**, Nogueira R, de Carvalho H. Behçet's syndrome and vesicovaginal fistula: an unusual complication. *J Urol* 1995; **153**: 407-408 [PMID: 7815600 DOI: 10.1097/00005392-199502000-00036]
159 **Davatchi F**, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, Faezi T, Ghodsi Z, Faridar A, Ashofteh F, Sadeghi Abdollahi B. Behcet's disease: from East to West. *Clin Rheumatol* 2010; **29**: 823-833 [PMID: 20354748 DOI: 10.1007/s10067-010-1430-6]
160 **Nakagawa H**, Namima T, Aizawa M, Uchi K, Orikasa S. [Three cases of neurogenic bladder due to neuro-Beçhet disease]. *Nihon Hinyokika Gakkai Zasshi* 1994; **85**: 1399-1402 [PMID: 7967304]
161 **Yurdakul S**, Mat C, Tüzün Y, Ozyazgan Y, Hamuryudan V, Uysal O, Senocak M, Yazici H. A double-blind trial of colchicine in Behçet's syndrome. *Arthritis Rheum* 2001; **44**: 2686-2692 [PMID: 11710724]
162 **Aktulga E**, Altaç M, Müftüoglu A, Ozyazgan Y, Pazarli H, Tüzün Y, Yalçin B, Yazici H, Yurdakul S. A double blind study of colchicine in Behçet's disease. *Haematologica* 1980; **65**: 399-402 [PMID: 6778795]
163 **Hatemi G**, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, Houman MH, Kötter I, Olivieri I, Salvarani C, Sfikakis PP, Siva A, Stanford MR, Stübiger N, Yurdakul S, Yazici H. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; **67**: 1656-1662 [PMID: 18245110 DOI: 10.1136/ard.2007.080432]
164 **Alizadeh F**, Khorrami MH, Izadpanahi MH, Nouri-Mahdavi K, Mohammadi Sichani M. Bladder involvement in Behcet's disease. *Urol J* 2012; **9**: 347-350 [PMID: 22395828]
165 **Norton EW**, Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms; a long-term follow-up. *AMA Arch Ophthalmol* 1959; **61**: 695-697 [PMID: 13636563 DOI: 10.1001/archopht.1945.00890140064007]
166 **Talar-Williams C**, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, Hoffman GS, Fauci AS, Sneller MC. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; **124**: 477-484 [PMID: 8602705]
167 **Fernandes ET**, Manivel JC, Reddy PK, Ercole CJ. Cyclophosphamide associated bladder cancer--a highly aggressive disease: analysis of 12 cases. *J Urol* 1996; **156**: 1931-1933 [PMID: 8911359 DOI: 10.1016/S0022-5347(01)65395-3]
168 **Knight A**, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 2002; **100**: 82-85 [PMID: 12115591 DOI: 10.1002/ijc.10444]
169 **Monach PA**, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum* 2010; **62**: 9-21 [PMID: 20039416 DOI: 10.1002/art.25061]
170 **Mukhtyar C**, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; **68**: 310-317 [PMID: 18413444 DOI: 10.1136/ard.2008.088096]
171 **Harper L**, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; **71**: 955-960 [PMID: 22128076 DOI: 10.1136/annrheumdis-2011-200477]
172 **Austin HA**, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; **314**: 614-619 [PMID: 3511372 DOI: 10.1056/NEJM198603063141004]
173 **Watson AR**, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. *Br Med J* (Clin Res Ed) 1985; **291**: 1457-1460 [PMID: 3933709]
174 **Fukutani K**, Ishida H, Shinohara M, Minowada S, Niijima T, Hijikata K, Izawa Y. Suppression of spermatogenesis in patients with Behçet's disease treated with cyclophosphamide and colchicine. *Fertil Steril* 1981; **36**: 76-80 [PMID: 6788612]
175 **Sarica K,** Suzer O, Gurler A, Baltaci S, Ozdiler E, Dincel C. Urological evaluation of behcet patients and the effect of colchicine on fertility. *Eur Urol* 1995; **27:** 39-42
176 **Blumenfeld Z**, Shapiro D, Shteinberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. *Lupus* 2000; **9**: 401-405 [PMID: 10981642 DOI: 10.1191/096120300678828596]
177 **Somers EC**, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005; **52**: 2761-2767 [PMID: 16142702 DOI: 10.1002/art.21263]
178 **Masala A**, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio PP,

Ivaldi R, Taras MS, Lai E, Bartoli E. Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997; **126**: 292-295 [PMID: 9036801 DOI: 10.7326/0003-4819-126-4-199702150-00005]

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