CASE REPORT

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# Fulminant Wegener's granulomatosis: A case report

## Fulminantna Wegener-ova granulomatoza

**Miroslav Ž. Dinić*, Lidija Kandolf Sekulović*†, Lidija Zolotarevski‡, Radoš D. Zečević*†**

***Clinic for Dermatovenerology, ‡Institute for Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia**

**Abstract**

**Introduction.** Granulomatosis Wegener is anti-neutrophil cytoplasmic antibodies (ANCAs)-associated systemic vasculitis of unknown etiology. It is manifested as granulomatous necrotizing inflammation of the upper and lower parts of the respiratory tract, glomerulonephritis and systemic vasculitis involving most frequently the skin and oral mucous membrane. Sera markers of this disease are c-ANCA and p-ANCA. **Case report**. We presented a female patient aged 52 years with purpuric spots that had appeared on the lower legs ten months before admission to our hospital. The disease ran an aggressive course, and a month before admission hemorrhagic bullae, skin ulcers, hoarseness, dyspnea, generalized arthralgia, fatigue and fever had rapidly developed. Histopathological examination of a skin sample revealed necrotizing vasculitis, so that sera markers concentrations were elevated (c-ANCA, p-ANCA). There was a perforation of the nasal septum found on rhinoscopy. During hospitalization acute abdominal pain occurred, a possible tumor in the small intestine and possible granulomas in the liver were seen by multislice computed tomography (MSCT) examination, with normal findings on the lungs and kidneys. The treatment started with methylprednisolone: 500 mg/d i.v. infusion for consecutive 3 days, then 60 mg/d. On exploratory laparotomy small bowel perforation and diffuse peritonitis were found. Unstable in the postoperative period, the patient died on the day 12 of hospitalization. **Conclusion**. The reported patient was with fulminant Wegener's granulomatosis, dominantly with skin changes and with gastrointestinal manifestation. This case accents the need for rapid systemic clinical evaluation in a severely ill patient with unclear diagnosis.

**Key words:**
**wegener granulomatosis; diagnosis; purpura fulminans; gastrointestinal diseases; histological techniques.**

**Apstrakt**

**Uvod.** Wegener-ova granulomatoza je sistemski vaskulitis nepoznate etiologije povezan sa prisustvom antineutrofilnih citoplazma antigen antitela (ANCA). Manifestuje se nekrotizujućom granulomskom upalom gornjih i donjih delova disajnih puteva, glomerulonefritisom i sistemskim vaskulitisom koji zahvata kožu i sluznicu usne duplje. Seromarkeri oboljenja su c-ANCA i p-ANCA. **Prikaz bolesnika.** Prikazana je bolesnica stara 52 godine, kojoj su se 10 meseci pre prijema u Kliniku pojavile purpurične mrlje na potkolenicama, a mesec dana pre prijema hemoragičke bule i ulceracije na koži, uz promuklost, dispnoju, bol u zglobovima, malaksalost i febrilnost. Histopatološkim pregledom uzorka izmenjene kože verifikovan je nekrotizujući vaskulitis, a koncentracije seromarkera su bile povišene: c-ANCA 18 IU/mL; p-ANCA 30 IU/mL. Uočena je i perforacija nosnog septuma. Tokom hospitalizacije javio se i bol u trbuhu, a pregledom multislajsnom kompjuterizovanom tomografijom (MSCT) viđen je mogući tumor na tankom crevu, kao i mogući granulomi u jetri, uz uredan nalaz na plućima i bubrezima. Započeto je lečenje metilprednizolonom 500 mg/d *iv* infuzijom tokom 3 dana, potom 60 mg/d. Eksplorativnom laparotomijom nađena je perforacija tankog creva uz difuzni peritonitis. Nestabilna u postoperativnom toku, bolesnica je preminula 12. dana hospitalizacije **Zaključak.** Prikazana je bolesnica sa Wegener-ovom granulomatozom fulminantnog toka sa dominantnim promenama na koži i gastrointestinalnom traktu. Ovaj slučaj naglašava potrebu za brzom sistemskom kliničkom procenom kod teškog bolesnika sa nejasnom dijagnozom.

**Ključne reči:**
**vegenerova granulomatoza; dijagnoza; purpura, fulminantna; gastrointestinalne bolesti; histološke tehnike.**

**Correspondence to:** Miroslav Ž. Dinić, Clinic for Dermatovenerology, Military Medical Academy, Crnotravska 17, 11000 Belgrade, Serbia. Phone: +381 11 3608 559. E-mail: miroslavdinic@hotmail.com

**Introduction**

Wegener granulomatosis (WG) is anti-neutrophil cytoplasmic antibodies (ANCAs)-associated systemic vasculitis of small arteries and veins of unknown etiology. It is manifested as granulomatous necrotizing inflammation of the respiratory tract, glomerulonephritis and systemic vasculitis involving most frequently the skin and oral mucous membrane. In the lungs, paranasal sinuses and nasopharynx nodular infiltrates can be found, with fever, weakness, sinus pain, or bloody or purulent discharge from the nose, cough, hemoptysis and dyspnoea. Skin lesions are found in 50% of patients; only 13% with initial skin changes, usually on the legs: pyoderma gangrenosum-resembling lesions, papules, vesicles, palpable purpura, subcutaneous nodules, plaques and noduloulcerous lesions resembling polyarteritis nodosa. Oral or nasal ulcers and/or perforation of the nasal septum can be presented on visible mucous membranes. The disease also affects the joints, kidneys, eyes and central nervous system (CNS) [1–4].

**Case report**

A female, aged 52 years, was admitted to the Clinic for Dermatology, Military Medical Academy in Belgrade, with a 10 month history of purpuric spots on the lower legs. One month before admission hemorrhagic bullae on the lower extremities and hands, skin ulcers of the right lower leg and thigh, abdomen and buttocks, hoarseness, dyspnea, generalized arthralgias, fatigue and fever up to 38°C had rapidly developed (Figures 1–4). By chest X-ray, performed few days before admission, nodular infiltrates were observed. There was a perforation of the nasal septum at the time of admission as seen by rhinoscopy. On the third day of hospitalization abdominal pain was reported. In laboratory analyses elevation of nonspecific inflammatory factors was evident [erythrocyte sedimentation rate (ESR) 63 mm/h, C-reactive protein (CRP) 263 mg/L], with a significant leukocytosis ($33.2 \times 10^9$/L) and neutrophilia (93.5%). Other blood count parameters, blood biochemistry, complement component 4 (C4) and liver enzymes serum activity were within normal range. C3 was decreased (0.6 g/L). In urinalysis hemoglobin and leukocytes were evident, with lot of sediment erythrocytes, leukocytes and bacteria, but urine culture was sterile, such as blood culture was. Concentration of 24-h urine protein was slightly elevated: 0.234 g (upper limit 0.15 g). ELISA human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) tests were negative. In peripheral blood smear increased number of leukocytes was evident ($55.7 \times 10^9$/L), as well as elevated percentage of neutrophiles (95%). Immunologig analysis revealed negative antinuclear antibodies (ANA) (HEp2 cell's substrate) and ENA screening tests, anticentromere antibodies (ACA) were within the physiologic range, but ANCAs were elevated (c-ANCA 18 IU/mL, p-ANCA 30 IU/mL). In direct immunofluorescence (DIF) of purpuric papule specimen IgM deposits in the basement membrane zone, fine- and coarse-grained deposits of C3 in the walls of blood vessels of the dermis were found.

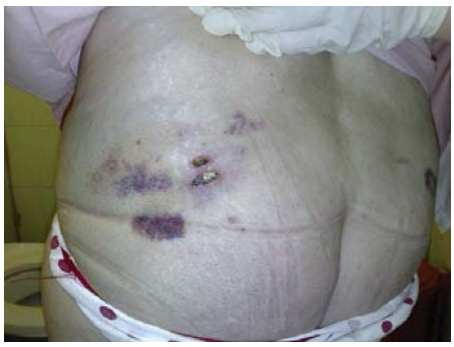

**Fig. 1 – Hemorrhagic bullae on the back.**

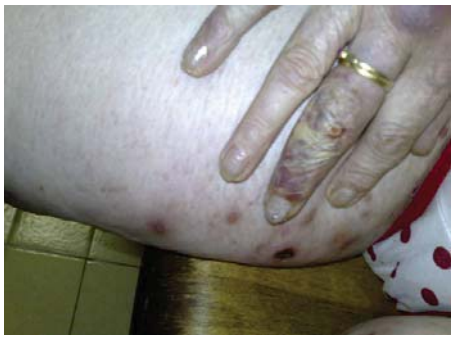

**Fig. 2 – Hemorrhagic bullae on the hands and skin ulcers on the right thigh.**

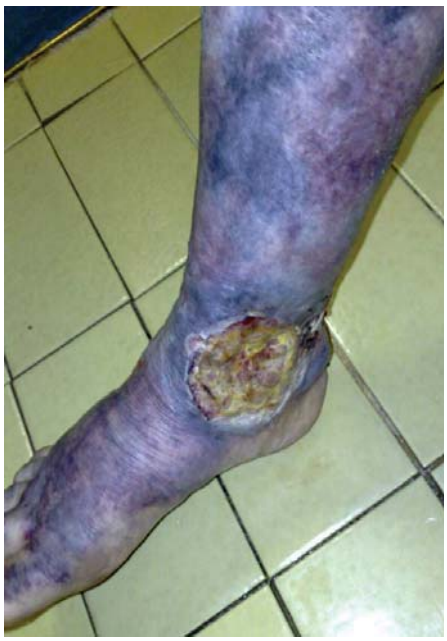

**Fig. 3 – Leg ulcers.**

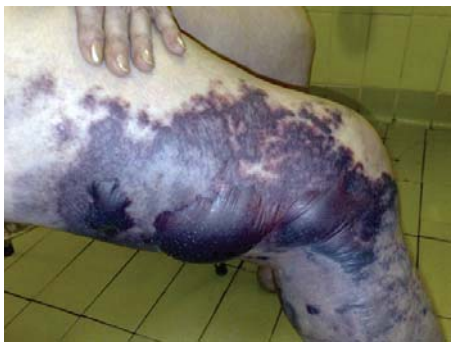

**Fig. 4 – Hemorrhagic bullae on the thigh.**

Histopathologic examination of the purpuric papule revealed necrotizing vasculitis of the skin (prominent extravascular neutrophilia and foci of suppuration in the dermo-subcutaneous border) (Figure 5). Histopathologic examination of nasal squamous mucosa revealed an acute inflammation. Ultrasound examination of the abdomen revealed dilated intestinal convolutions with proper findings on liver, gallbladder, spleen and kidneys, but certain amount of ascites. Esophagogastroduodenoscopy revealed ulceration on a small curve diameter of 5 mm, the bottom covered with white patches of scum from the edge dark crust (biopsy was not performed). MSCT of the chest and abdomen revealed right lung bullous formation of 2 cm in diameter at the top of the upper lobe, a number of possible granulomas in the liver, abdominal cavity was dominated by the free gas and the presence of free intraabdominal fluid, with a finding on the small bowel which may correspond to tumor formation or small intestine curve in volvulus. Based on skin changes, nasal perforation and positive c- and p-ANCA, in consultation with other specialists (rheumatologist, pulmologist, otolaryngologist) diagnosis of WG was established and the therapy with a pulse dose of methylprednisolone (500 mg/d i.v., for 3 consecutive days) and 60 mg/d i.v. after pulse dose was administred. Other therapy included: systemic antibiotics (metronidazole, ciprofloxacine), analgesics, antipyretics, fluconazole and pantoprazole gastroprotective therapy. Because of a possible tumor in the small intestine revealed by MSCT examination and the possible development of surgical abdomen (strong abdominal pain) exploratory laparotomy was performed on the day 6 of hospitalization, in which a small bowel perforation was found with diffuse peritonitis. Unstable in the postoperative period, the patient died on the day 12 of hospitalization due to peritonitis.

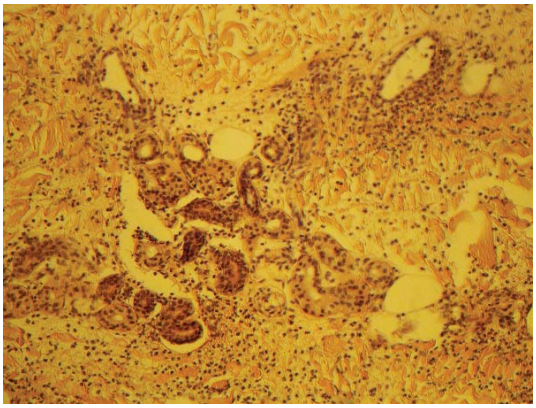

**Fig. 5 – Histopathological finding of the purpuric papule – prominent extravascular neutrophilia, and foci of suppuration in the dermo-subcutaneous border (N&E, ×20).**

## Discussion

In 1930s, Wegener described 3 patients in their 30s with granulomatous vasculitis affecting the nose and throat, lungs and kidneys. The syndrome became known as 'Wegener's granulomatosis [1]. Untill 1980s, the significance of the association of c-ANCA with WG was not recognized. The incidence of WG is estimated to be 5 to 12 cases per million, with a slight female predominance [2]. Classic WG is the triad of granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing small vessel vasculitis and immune glomerulonephritis. Patients with classic WG have a high mortality rate if left untreated, whereas patients with limited forms have isolated features of the triad and less severe involvement [3]. Mucocutaneous involvement occurs in approximately 40% of patients with WG, and it can be the presenting sign in 10% [4]. The most common lesions are palpable purpura, followed by oral ulcers. Skin changes that resemble pyoderma gangrenosum can also be seen. The upper or lower respiratory tracts are involved in up to 90% of patients with WG. Nasal involvement is responsible for presenting complaints in greater than 70% of cases. Suggestive symptoms and signs include recurrent epistaxis, mucosal ulcerations and nasal septal perforation. Patients with pulmonary involvement present with dyspnea, cough, hemoptysis or pleuritis, and chest X-rays demonstrate infiltrates or nodules. Approximately 75% of patients eventually develop glomerulonephritis [5]. Other organ systems commonly affected in WG include musculoskeletal (70%), ocular (30–60%), neurologic (20–50%) and gastrointestinal (5–10%). Most common gastrointestinal manifestations include: abdominal pain, nausea/vomiting, diarrhea, hematochezia or melena. Elevated c-ANCA occurs in approximately 80% of patients with classic or severe WG, but only in 60% of patients with limited disease, and p-ANCA occurs in approximately 10% of WG patients [3]. The majority of skin biopsy specimens show nonspecific histopathologic changes, but up to 50% demonstrate leukocytoclastic vasculitis and/or granulomatous inflammation. The mainstay treatment for patients with classic WG is systemic corticosteroids in conjunction with cyclophosphamide, resulting in a remission in up to 75% of patients [5]. In our patient, skin changes, nasal septum perforation, small bowell perforation due to vasculitis and occuring of ANCAs established the diagnosis of WG. Lethal outcome occurred due to diffuse peritonitis. Most common symptoms and signs of a small-vessel vasculitis of the gastrointestinal tract are abdominal pain, diarrhea and hematochezia. The frequency of gastrointestinal manifestations in WG is actually uncertain, because of small number of documented severe disease case reports [6, 7]. A study involving 45 patients found abdominal symptoms in 4 of them [6]. Severe gastrointestinal involvement manifested during the early stages of WG, particulary without concomitant renal disease is very rare, just few cases were previously reported, but without lethal outcome [7, 8]. In a study of Pagnoux et al. [9], presentation and outcome of gastrointestinal (GI) involvement in systemic necrotizing vasculitis were evaluated – a group of 62 patients with systemic small and medium sized vessel vasculitis and GI involvement: polyarteritis nodosa (total of 38), Churg Strauss syndrome (total of 11), WG (total of 6), microscopic polyangiitis (total of 4) and rheumatoid arthritis-associated vasculitis (total of 3). GI manifestations were present at or occured within 3 months of establishing diagnosis in 81% of the patients: abdominal pain (97%), nausea or vomiting (34%), diarrhea (27%) and hematochezia or melena (16%).

Further, 34% patients devoloped surgical abdomen, 18% peritonitis, 15% bowel perforation, 16% bowel ischemia/infarction and 6% intestinal occlusion. Peritonitis, bowel perforations, GI ischemia/infarctions and intestinal occlusion were the only GI manifestations significantly associated with increased mortality (for this group of patients 6-month and 5-year survival rates were 60% and 46%, respectively). But, in the subgroup of WG patients none of severe GI manifestations related with increased mortality were evident. The most severe manifestations in WG (total of 6) were esophageal (total of 1), gastroduodenal (total of 2) and colorectal (total of 2) ulcerations, without lethal outcome due to GI manifestations.

## Conclusion

Our patient showed severe gastrointestinal and skin features, fulminant course and lethal outcome. This confirms the necessity for rapid systemic clinical evaluation in any critically ill patients with unclear diagnosis.

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