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Case Report

Pancytopenia Due to Cytomegalovirus Infection in a Man with Wegener's Granulomatosis Treated Successfully

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Case Summary

A 32-year-old man presented with myalgia, polyarthritis, hearing problem, sneezing, erythematous rash and episcleritis for one month. He was diagnosed as Wegener's Granulomatosis and c-ANCA was positive. Then, he had rapidly progressive renal failure due to pauci immune crescentic glomerulonephritis and ARDS. Therefore, aggressive immunosuppressive therapy was initiated which included oxygen therapy, corticosteroids, cyclophosphamide and rituximab. Six weeks after completion of immunosuppressive therapy, he had pancytopenia. Cytomegalovirus (CMV) viral load was 5653.0Copies/ml and he was treated with intravenous ganciclovir. Six-weeks later, full blood count returned to normal; and, CMV viral load was undetectable.

Keywords: Pancytopenia, Cytomegalovirus (CMV) infection, Wegener's Granulomatosis, c-ANCA

Introduction

Wegener's Granulomatosis (WG) is an uncommon autoimmune disease characterized by granulomatous inflammation of the respiratory tract and systemic small vessel vasculitis that is usually associated with significant morbidity and mortality. The diagnosis of WG is made based on clinical features of illness associated with the presence of c-ANCA (anti-neutrophil cytoplasmic antibody) and vasculitis in small arteries and veins, with the presence of giant cells and epithelioid cell granulomas. The onset of WG is usually insidious, and the diagnosis is often delayed with potential life-threatening progression. Common presenting features of WG were reported

as glomerulonephritis (88%), diffuse alveolar hemorrhage (44%) and venous thrombotic events (12%). Here, we report a case of WG having pancytopenia and transaminitis.

Pancytopenia is a relatively common phenomenon encountered in clinical practice. It has several impact and various underlying causes: drugs; autoimmune conditions; malignancies; infections; hemophagocytosis; and inheritable conditions. Therefore, the evaluation of a patient with pancytopenia was challenging [1,2]. Moreover, the severity of pancytopenia and the underlying pathology determine the management and prognosis. Thus, comprehensive clinical and hematological evaluation of pancytopenia cases will help in identification of the correct cause and in implementing the appropriate therapy [3-5]. There were several case reports on ANCA-associated vasculitis with pancytopenia due to vasculitis involving bone marrow [6]; with pulmonary involvement [2]; with renal involvement [7,8]; with intestinal involvement [9]. CMV infection producing pancytopenia was common [10,11]. Here, we report a case of ANCA-associated vasculitis Wegener's Granulomatosis with pancytopenia due to CMV infection.

Case Presentation

A 32 years old doctor was previously healthy till September 2023. He had sneezing, feeling of blockage in both ears more on right and epistaxis for 1 week duration; and, he was treated as a case of acute suppurative otitis media. He was given Augmentin 625mg 3 times a day for 10 days and topical nasal steroid. It was followed by episcleritis of left eye, myalgia and polyarthritis involving large joints: both knee joints, elbow joints, multiple joint pain especially in large joint. They were swollen; very tender; non-migratory in nature; and, disturbing sleep even with diclofenac 50mg 3 times a day. The clinical impression was acute polyarthritis due to virus (Chikungunya infection) or bacterial (acute rheumatic fever) in etiology. Blood for complete picture showed normal total WBC count, hemoglobin and platelet count. Inflammatory markers were raised; ESR was 10mm in 1st hour; and CRP 6.7. ASO titer was 200units; serum creatinine was normal 0.93mg/dl; uric acid 7.4mg/dl. Anti-CCP was negative and RA test was positive. As RA test was positive; the likelihood of seropositive RA was considered though several points were against it. They were male sex; relatively short duration of joint symptoms of less than 2 weeks; involvement of large joints. Rheumatologist suggested to start steroids, methotrexate, calcium supplements for possible seropositive rheumatoid arthritis and allopurinol for hyperuricemia.

One month later, erythematous maculo-papular rash appeared on both shin and chest. It is shown in Figure 1 and 2. Then, he had puffy face; serum creatinine suddenly rose to 7.2mg/dl. His urine output was normal. Meanwhile, he was having low grade fever. Full blood count showed normal; total WBC count was upper normal limit (12X109/L); hemoglobin was 12.9gm/dl; platelet count was 406X109/L. ANA was negative. Inflammatory markers were rising rapidly; ESR became high (70mm in 1st hour); CRP rose to 89. Uric acid was remained high 8.2mg/dl; liver function tests were normal; and random blood sugar was 103mg/dl. Blood urea was very high 142mg/dl; and, serum creatinine was very high to 7.2mg/dl; serum potassium was 5.58mg/dl. Chest radiograph was normal. Ultrasound kidney was suggestive of bilateral mild nephropathy. In ANCA testing, p-ANCA was negative and c-ANCA was positive. Regarding ANCA profile, both Proteinase 3 and Myeloperoxidase were negative. Renal biopsy was suggestive of a pauci-immune crescentic glomerulonephritis. He was given aggressive treatment to save kidney with rituximab, methylprednisolone and cyclophosphamide (Figure 1,2).

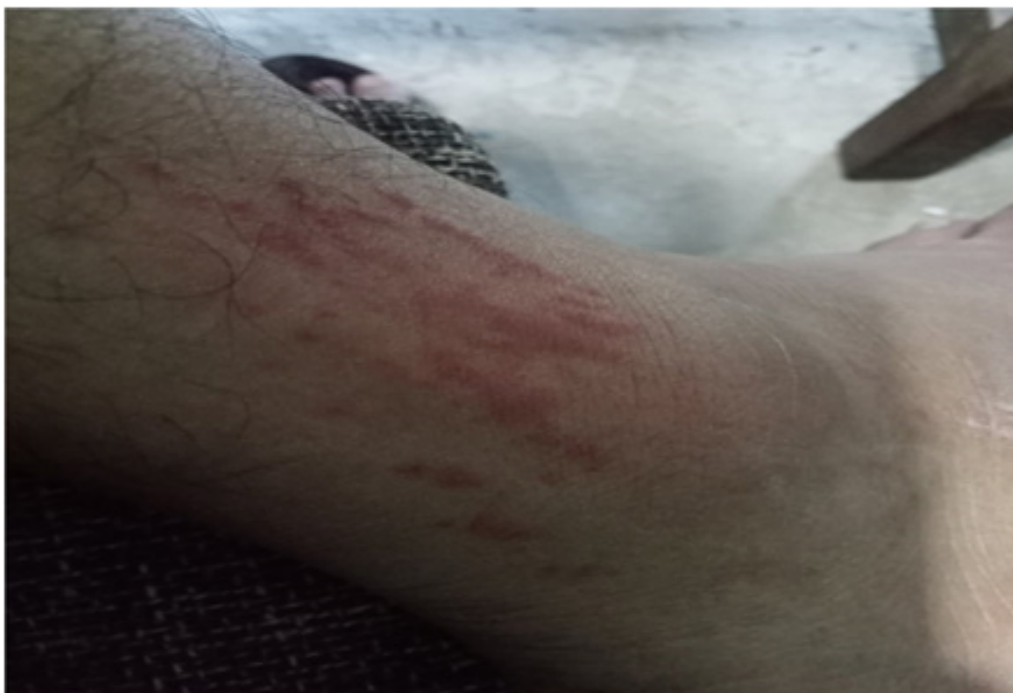

Figure 1: Erythematous rash over shin.

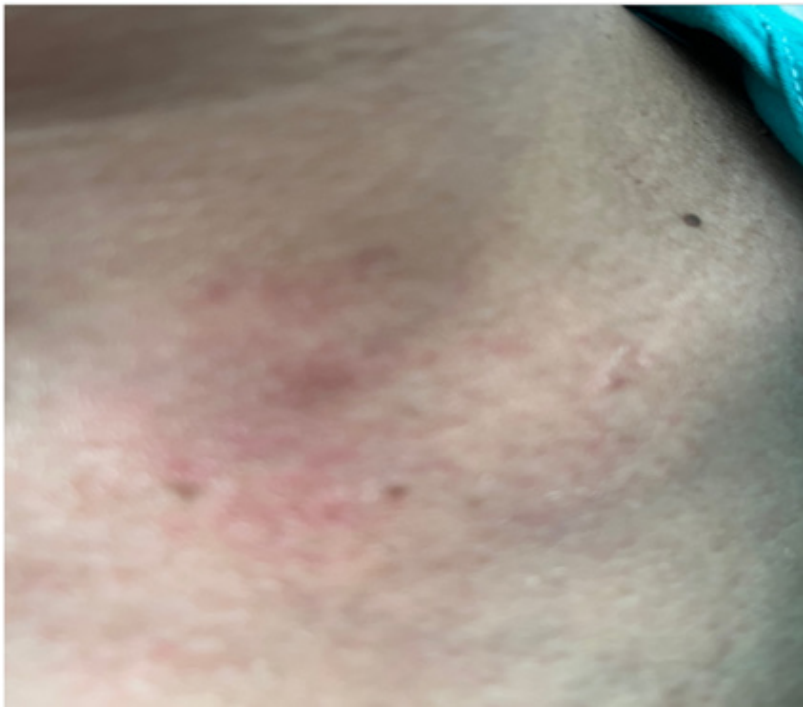

Figure 2: Erythematous rash over chest.

While giving aggressive immunosuppressive therapy to retard rapidly progressive glomerulonephritis and renal failure, he continued to have oliguria, rising serum creatinine and fluid overload. Therefore, hemodialysis was initiated on after fourth dose of rituximab. Then, he developed ARDS; he was treated with oxygen therapy, intravenous methylprednisolone and antibiotics. All full blood counts were low at the time of diagnosis of ARDS; hemoglobin dropped dramatically from 12.9gm/dl to 7.0gm/dl; total WBC count decreased from 12X109/L to 2.4X109/L; platelet count reduced from 406X109/L to 80X109/L. The timing of pancytopenia was 6 weeks after completion of immunosuppressive therapy. Blood film revealed normochromic normocytic anemia, spherocyte, polychomasia and schistocyte. Figure 3 and 4 shows blood film. Liver enzymes were marginally increased (Figures 3,4). CMV viral load was quantitative PCR-5653.0Copies/ml (28.3.2024). Therefore, intravenous ganciclovir 62.5mg (1.25mg/kg) was initiated 3 times per week for 3 weeks; it was given at the end of hemodialysis. Platelet infusion and packed cell transfusion were given; serial monitoring of full blood parameters was done. It is demonstrated in (Table 1). Two weeks after anti-viral treatment, all cell line improved gradually. Total WBC count and platelet count became normal at 6 weeks after anti-viral therapy. Six weeks after anti-viral therapy, CMV viral load was undetectable. Apart from anemia which was caused by end stage renal disease, both total WBC and platelet were normal till now (8 months after anti-viral drugs). He was waiting for living donor kidney transplant.

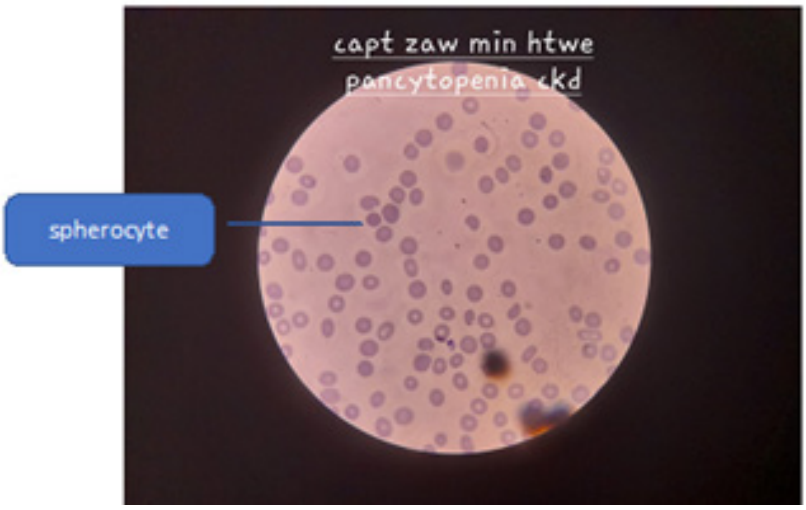

Figure 3: Peripheral blood film showing spherocyte.

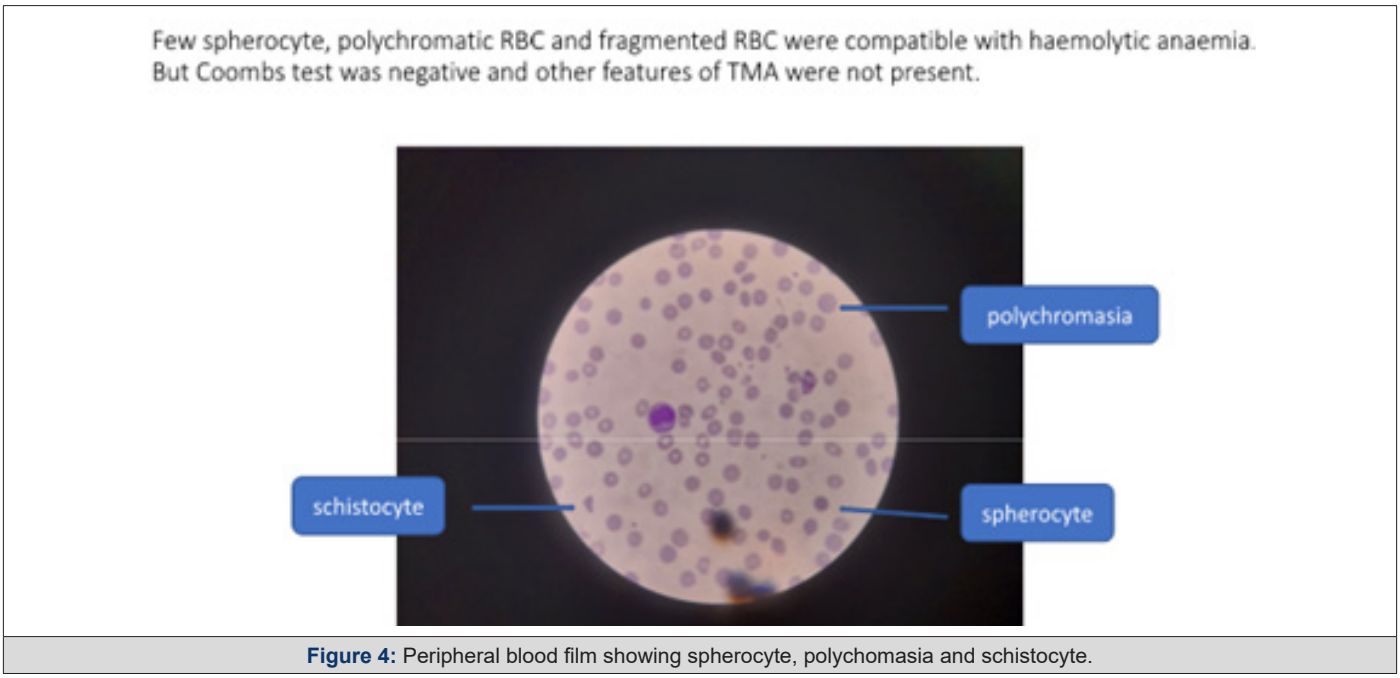

Figure 4: Peripheral blood film showing spherocyte, polychomasia and schistocyte.

Table 1: Serial hematological & biochemical parameters.

Date	Sept-2023	Dec-2023	Early Feb 2024	End Feb 2024	Early March 2024	End March 2024	April-2024	May-2024	June-2024	July-2024	Aug-2024	Sept-2024
Hb (gm%)	12.9	14.9	6.9	8.1	8.3	7.9	8.9	11	8.3	7.4	10.3	9.7
TWBC ($X10^9/L$)	8	6.3	2.4	2.1	1.7	3.6	3.2	4.7	6.4	5.6	7.3	6.1
ALC ($X10^9/L$) (0.8-4.0)		1.2	0.2	0.3	0.2	0.3	0.4	1	0.7	0.6	1	0.9
Neutrophil ($X10^9/L$) (2.0-7.0)		4.9	2	1.9	1.5	3	2.5	3.2	5.2	4.4	5.8	4.8
Platelets ($X10^9/L$)	300	331	270	170	146	209	124	151	170	140	175	194
Bilirubin												
SGPT (U/L)	20	25	53		22.7							
SGOT (U/L)	20	25	29.6		24.8							
Albumin (gm/L)	35		28.6									
Total protein (gm/L) (62-80)			42.8									

Discussion

Wegener's Granulomatosis, (WG) is an inflammatory disorder of presumed autoimmune pathogenetic mechanism characterized by granulomatous inflammation of the respiratory tract, necrotizing vasculitis, and glomerulonephritis. However, the disease can affect any organ and shows diverse clinical manifestations. Anti Neutrophil Cytoplasmic Antibodies (c-ANCA) are strongly associated with the pathogenesis and diagnosis of WG. The clinical presentation may simulate an atypical infection or other autoimmune or hematologic diseases. The initial symptoms in this patient involved eye, ear, respiratory tract and kidney. As he had rapidly progressive pauci-immune glomerulonephritis with c-ANCA positive and rapidly rising serum creatinine, aggressive immunosuppressive therapy was initiated. The serum creatinine became rising during treatment; therefore, he underwent hemodialysis. At the same time, he had features of ARDS; oxygen therapy and continuous positive airway pressure were given. His full blood count was falling rapidly over one month, pancytopenia; it began 6 weeks after completion of immunosuppressive therapy.

Pancytopenia is a reduction in the number of red blood cells, white blood cells, and platelets in the peripheral blood. Pancytopenia may result from decreased production of blood cells due to bone marrow failure, or from immune-mediated destruction of blood cells, or non-immune-mediated sequestration in the periphery/spleen. It has several impact and various underlying causes: drugs; autoimmune conditions; malignancies; infections; hemophagocytosis; and inheritable conditions. Therefore, the evaluation of a patient with pancytopenia was challenging [1,2,12]. Moreover, the severity of pancytopenia and the underlying pathology determine the management and prognosis. Thus, comprehensive clinical and hematological evaluation of pancytopenia cases will help in identification of the correct cause and in implementing the appropriate therapy [3-5].

In this patient, the likely causes of pancytopenia were as follows: (1) WG affecting bone marrow [13]; (2) disseminated intravascular coagulation (DIC); (3) myelotoxicity of cyclophosphamide; (4) myelotoxicity of rituximab; and, (5) CMV infection. WG is also a systemic disease that can lead to systemic, cytokine-mediated reactions. Because bone marrow contains a range of blood vessel types, including small arteries, it could be susceptible to the same diseases that affect blood vessels elsewhere in the body. WG affecting bone marrow as part of systemic manifestation was possible; it was reported by several studies [14,6]. Bone marrow examination showed reduction in precursors of all 3 cells lines; and it was responsive to immunosuppressive therapy. However, finding evidence of vasculitis or a granuloma in bone marrowy a blind biopsy in WG patients was not easy. ANCA associated vasculitis causing pancytopenia was reported to be responsive to immunosuppressive therapy [15,2]. Opportunistic infections should always be considered as a cause of cytopenias when immunosuppression is present.

DIC was another possible cause in this patient because he had ARDS which might result from infection or WG itself. This patient did not have fever; blood culture was negative; sputum was not productive; urine culture was sterile. Therefore, DIC was less likely cause of pancytopenia in this case. Side effect of cyclophosphamide causing pancytopenia was extremely rare as the onset of pancytopenia in this case was 6 weeks after completion of immunosuppressive therapy. According to [16], intravenous cyclophosphamide and SLE disease activity had independent effects in lowering white blood cell counts; however, serious myelotoxicity of intravenous cyclophosphamide was uncommon [16]. Intravenous cyclophosphamide was used in severe aplastic anemia, a life-threatening bone marrow failure disorder, to get bone marrow recovery [17-19]. Only one report mentioned pancytopenia due to cyclophosphamide following treatment with breast cancer [20].

Bone marrow suppressant effect of rituximab producing pancytopenia was unlikely as the onset of action of rituximab was 6 weeks after treatment. Several recent studies reported the phenomenon of late-onset neutropenia occurring usually several months following the administration of rituximab or rituximab-based therapies; nonetheless, it was not clinically significant and self-limiting [21]. Rituximab was an effective non-myelosuppressive treatment [22,23]. Therefore, myelosuppressive effect of rituximab producing pancytopenia in this patient was unlikely. In this patient, CMV infection caused pancytopenia. *Uslu Yurteri, et al.,* pointed out that renopulmonary involvement was one of independent risk factors of infection in ANCA-associated vasculitis [24]. Having renopulmonary involvement in this patient was thought to be vulnerable to CMV infection. Moreover, analysis on risks of infection in ANCA-associated vasculitis by Alvarez Troncoso showed that pancytopenia was a risk factor for infection both bacterial and opportunistic infection [13]. CMV infection producing pancytopenia was found in several reports [10,11]. Having CMV viral load of 5653.0 Copies/ml at the time of pancytopenia; and, undetectable viral load after 6 weeks course of ganciclovir was the proof for CMV infection. Liver enzymes were slightly high initially and they became normal after completion of ganciclovir therapy; it was another supportive evidence. CMV hepatitis was common both in immunocompetent and immunocompromised hosts [25].

Pancytopenia secondary to reactivation of CMV was reported by Tse & Ng [26]. CMV infection as a result of reactivation due to immunosuppressive treatment in patients with WG was common. CMV reactivation was possible as ASIAN population had relatively high prevalence of CMV infection [27-30] (*Prevalence and Recurrence Rates of Cytomegalovirus Infection Among Patients with Hematological Diseases in the Western Brazilian Amazon: A Cross-Sectional Study, n.d.*) [31]. The predictors of CMV viremia and infection after the start of induction of immunosuppressive therapy for patients with ANCA-associated vasculitis were analyzed in some studies [32]. In patients with rheumatic disease, old age, high creatinine, hypoalbuminemia and cyclosporin therapy were prone to CMV infection [33]. This patient had all predictors for CMV viremia and infection; total protein was low normal; low serum albumin; high serum creatinine; low hemoglobin; low absolute lymphocyte count; and thrombocytopenia [34,35].

Conclusion

Pancytopenia is not rare in clinical practice. CMV infection producing pancytopenia is not uncommon. Reactivation of CMV infection should be consider in cases with ANCA-associated vasculitis Wegener's Granulomatosis, immunocompromised patients particularly those with positive predictors. Early diagnosis and prompt treatment may make bone marrow recovery. Multidisciplinary collaboration was crucial in managing the multifaceted clinical condition of the patient.

Ethical Consideration

Informed consent was taken from patient.

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Conflict of Interest

None.

Funding

None

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