

Reactive Large Granular Lymphocyte (LGL) proliferation secondary to Granulomatosis with Polyangiitis (GPA) – A Case Report

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Citation: Piazera FZ (2020) Reactive Large Granular Lymphocyte (LGL) proliferation secondary to Granulomatosis with Polyangiitis (GPA) – A Case Report. American Journal of Surgery and Clinical Case Reports. V2(1): 1-6.

Received Date: July 27, 2020 **Accepted Date:** Aug 28, 2020 **Published Date:** Sep 03, 2020

1. Abstract

A 30-year-old male presented to the hematologist with signs suggestive of recurrent infections and no evidence of organ enlargement. Laboratory testing revealed severe neutropenia and elevated CRP, ESR and β 2-microglobulin as well as hypergammaglobulinemia. There were no signs of anaemia and rheumatoid factor was slightly elevated. Immunophenotyping by flow cytometry revealed T-cell proliferation with LGLL phenotype. Treatment was initiated with different single-agents MTX, CYC and cladribine, all of which presented unsatisfactory outcomes. After 3 years of partial but stable clinical response, the patient developed dermatological lesions that triggered an alternative diagnosis suspicion. He underwent diagnosis reinvestigation which revealed polyclonal expansion of LGL rather than monoclonal, rescinding his previous LGLL diagnosis. Further testing revealed c-ANCA positivity although MPO and PR3 were negative. Renal function was normal and there was no evidence of pulmonary involvement. Later he developed pneumonitis with elevated CRP and a positive atypical c-ANCA with a very high titre. Renal function remained normal, but new clinical presentation prompted a diagnosis of GPA, which in this case presented as a LGL polyclonal proliferation with symptoms similar to LGLL. New therapeutic approach was made with good clinical response.

2. Keywords

Large granular lymphocyte leukemia; Large granular lymphocyte; Wegener's granulomatosis; Granulomatosis with polyangiitis

3. Abbreviations: GPA: Granulomatosis with Polyangiitis; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; LGL: Large Granular Lymphocyte; LGLL: Large Granular Lymphocyte Leukemia; ANC: Absolute Neutrophil Count; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; MTX: Methotrexate; CYC: Cyclophosphamide; CBC: Complete Blood Count; IF: Indirect Immuno Fluorescence; PR3: Proteinase 3; MPO: Myeloperoxidase; TCR: T-Cell Receptor; eGFR: Estimated Glomerular Filtration

Rate; CyA: Cyclosporine A; AAV: ANCA-Associated Vasculitis; MPA: Microscopic Polyangiitis; EGPA: Eosinophilic Granulomatosis with Polyangiitis; CHCC: Chapel Hill Consensus Conference; ACR: American College of Rheumatology.

4. Introduction

Granulomatosis with polyangiitis (GPA) is an autoimmune small vessel vasculitis characterized by the presence of Anti-Neutrophil Cytoplasmic Antibodies (ANCA). It can cause granulomatous inflammation, as well as respiratory and renal symptoms. In this case report, we describe a case of GPA manifested initially as a Large Granular Lymphocyte (LGL) proliferation thought to be, at first glance, LGL Leukemia (LGLL). Although the disease has a variety of manifestations that presented herein is very unlikely. Few cases similar to this have been reported in a study with 11 case reports of LGLL associated with different vasculitis (mainly small vessel vasculitis), but none of them were related to GPA neither included LGL polyclonal proliferation (which was our case) but rather monoclonal proliferation only [1].

We will initially describe the case and then review the current concepts regarding LGLL and GPA, making correlation with the clinical presentation that our patient had and pointing out the atypical features.

5. Materials and Methods – Case Report

A 30-year-old male patient presented to the hematology medical service at the end of 2011 with complaints of acne re-emergence on the face and the back as well as recurrent constitutional symptoms, such as fever and malaise. Patient did not had signs of hepatosplenomegaly on physical examination. Laboratory testing showed a severe neutropenia with an absolute neutrophil count (ANC) < 200 cells/mm³, an elevated C-Reactive Protein (CRP) of 11,08 mg/dL and a slightly elevated Erythrocyte Sedimentation Rate (ESR) of 17 mm/h. It also revealed a markedly elevation in β 2-microglobulin of 3964,0 ng/mL, as well as hypergammaglobulinemia on serum

protein electrophoresis with increased IgG (1859 mg/dL) and IgM (332,0 mg/dL) and decreased albumin (3,48 g/dL) and IgA (2,0 mg/dL). There were no signs of anaemia or thrombocytopenia and rheumatoid factor was slightly elevated.

Further testing revealed a normal male karyo type and an immunophenotyping by flow cytometry of a patient's sample from the bone marrow was conducted. It revealed a lymphocytic proliferation almost exclusive of T-cells, of which 89% were CD2+, CD4-, CD5dim, CD8+, CD16-, CD57+, CD56- and TCR $\alpha\beta$ +. This T-cell phenotype was suggestive of LGLL, which alongside the typical clinical presentation of the patient and his other laboratory results prompted a diagnosis of LGLL at the time, even though clonality was not assessed.

Therapy was then initiated in 2012 with methotrexate (MTX) alongside prednisone as a first option due to agranulocytosis and recurrent infections. Patient's clinical course sustained partial response for 6 months with raise in ANC > 500 cells/mm³ and no novel infections. Seeking better results, MTX was switched to Cyclophosphamide (CYC) mono therapy in July of that same year. Patient's clinical response to CYC declined 6 months later in January of 2013, with worsening of the neutropenia and development of lymphocytosis.

After these 2 absences of complete clinical response, a new immunophenotyping by flow cytometry was conducted to reassess the diagnosis and the result confirmed the previous LGLL diagnosis with the same T-cell phenotype discovered before. Following the recommendations from the "How I Treat" journal, therapy was then switched to the purine analog cladribine [2]. We conducted 1 cycle with partial response and relapse within 3 weeks. Patient then returned to treatment with prednisone, with posterior tapering, alongside weekly G-CSF in order to improve neutrophil count. It is worth noting that within the last 6 months, he presented with 3 pneumonia episodes due to neutropenia. He had a sustained partial response with ANC > 1500 cells/mm³ and reduction in lymphocytosis, maintaining this therapeutic approach for over 3 years with a stable clinical course.

However, in 2016, our patient began to present erythematous pustules and papules in the axillary region (Figure 1). These lesions, alongside the patient's absence of complete clinical response and several unsatisfactory results with different therapeutic approaches, prompted us starting to take into consideration that LGLL probably was not his true diagnosis. In this context, patient underwent diagnosis reinvestigation while maintaining previous drug therapy of prednisone and weekly G-CSF. Complete Blood Count (CBC) revealed a neutropenia persistency in a leukopenia context, the latter probably due to the long-term corticosteroid therapy, and a mild thrombocytopenia of 108,000/mm³. An intestine biopsy showed no signs of inflammatory disease and other laboratory results discarded HIV and rheumatic disease. Despite that, c-AN-

CA positivity on indirect Immune Fluorescence (IF) triggered suspicion around a possible diagnosis of GPA, although patient's enzymatic fluoroimmunoassay didn't show a positive Proteinase 3 (PR3) or Myeloperoxidase (MPO) neither he had clinical signs nor laboratory results suggestive of renal or pulmonary involvement, since serum creatinine never surpassed 1,00 mg/dL, blood urea usually ranged around 25-35 mg/dL and chest and abdomen computed tomography revealed no lesions or organ enlargement. Also, the skin lesions that appeared on that same year were not characteristic of vasculitis.



Figure 1: Erythematous pustules and papules in the axillary region

Later, a new immunophenotyping was conducted in 2017 to assess the clonality of the T-cell population located in the bone marrow through V β T-Cell Receptor (TCR) gene repertoire analysis on flow cytometry. That confirmed our suspicion that LGLL was not his true diagnosis since there was no evidence of clonality. Therefore, the patient's clinical course represented a reactive LGL polyclonal proliferation secondary to an unknown pathogenic process.

This clinical scenario of diagnosis uncertainty persisted until 2019, when the patient was admitted to a hospital facility with a pneumonitis suspicion. Laboratory testing at the time revealed a leucocytosis of 17.000 cells/mm³, with proliferation of neutrophils (12.240 cells/mm³) and monocytes (2.040 cells/mm³), as well as an elevated CRP of 14,4 mg/dL and a positive atypical c-ANCA with a very high titre. Despite the c-ANCA result, enzymatic fluoroimmunoassay continued to show a negative PR3 and MPO autoantibody result. Renal function was normal, with a serum creatinine of 0,85 mg/dL, an estimated glomerular filtration rate (eGFR) above 90 ml/min/1,73m² and a blood urea between 25-35 mg/dL. After patient stabilization, a chest and face computed tomography was performed and revealed small and sparse pulmonary calcifications bilaterally and mucosal thickening of the sinus, suggestive of rhino sinusitis.

This new clinical course alongside the new laboratory and image results prompted a new diagnosis in 2020 of GPA with a secondary reactional LGL proliferation. Patient was referred to a rheumatologist, which then confirmed the diagnosis and initiated MTX therapy alongside prednisone to treat the GPA, whereas we con-

tinued to evaluate the patient regularly to assess his neutrophil count through laboratory testing and administer G-SCF in case of severe neutropenia. Since then, patient has sustained a good clinical course with a neutrophil count of 2700 cells/mm³ and without recurrent infections.

6. Results and Discussion

6.1. Large Granular Lymphocyte Leukemia (LGLL)

LGLL is a rare chronic lymphoproliferative disorder of T-cell and NK-cell lineage characterized by clonal expansion of LGL with resistance to apoptosis alongside bone marrow, liver and spleen tissue infiltration [2, 3]. These LGL are characterized on blood smears by their large size, abundant cytoplasm with azurophilic granules containing perforin and granzyme Band reniform or round nucleus [2]. It is a rare disease that accounts for 2-5% of chronic lymphoproliferative disorders in North America with equal incidence in males and females and primarily affecting the elderly people around 60 years-old, even though our patient was presumptively in the small 10% group younger than 40 years-old affected by LGLL [3, 4].

The disease is classified into 3 categories: aggressive NK-cell LGLL (< 5% of cases), NK-cell lymphocytosis (< 10% of cases) and chronic T-cell LGLL (~85% of cases), the latter 2 with indolent and similar clinical courses and treatment options [3]. Aetiology is still unknown, but the mature post-thymic phenotype that reflects a constitutively activated T-cell cytotoxic population suggests a chronic antigen exposure, hence inducing an antigen-driven clonal selection of leukemic LGL, even though which antigens cause that is still a matter of debate [2, 4]. This persistent antigen exposure causes Stat3 activation and mutation with gain-of-function in the long-term, causing constitutively activation of the Stat3 pathway [3]. Though important in the leukemogenesis of the disease, this mutation is detected in 28-75% of patients and there are other survival cell pathways that are also dysregulated [3].

This monoclonal LGL population induces disease manifestations through proinflammatory cytokine production and release of cytotoxic granules containing perforin and granzyme B [3]. Furthermore, leukemic LGL cell survival is supported by the IL-15, IL-12 and platelet-derived-growth factor secretion, which play a role in leukemic LGL proliferation and cytotoxicity [3, 4]. Moreover, although LGL present with an antigen-activated T-cell phenotype with Fas and Fas-L up regulation, the clone cells are resistant to Fas-induced cell death, contributing to clonal expansion [4]. The mechanism underlying this apoptosis resistance may be a defective IL-2 production, since it predisposes peripheral T-cells to Fas-mediated apoptosis [4]. Also, high levels of soluble Fas-L may be responsible for tissue damage and cytopenia, especially neutropenia, as well as possible autoimmune processes mediated through anti-neutrophil antibodies that arise from impaired down regulation

of Ig secretion, the latter evidenced by the frequent hypergammaglobulinemia, although neutropenia mechanisms in the disease are not fully understood [3, 4].

About 2/3 of patients are symptomatic at diagnosis and they can present with fatigue and neutropenia associated with recurrent infections, which were present at our patient's initial clinical course. However, he did not present with other common clinical features, such as splenomegaly, B symptoms, anaemia, associated autoimmune diseases (most frequently rheumatoid arthritis) or lymphocytosis at first, even though the latter he presented later in 2013 [3, 4].

There were also laboratory results that suggested LGLL diagnosis, such as high β 2-microglobulin and rheumatoid factor, presented in 70% and 60% of patients, respectively [3, 4]. He also had polyclonal hypergammaglobulinemia, further reinforcing the diagnosis suspicion. Although definite diagnosis is made through evidence of clonality from circulating LGL through PCR analysis of TCR or through analysis of V β repertoire of the TCR gene on flow cytometry, we concluded our first diagnosis in the context of lymphoproliferation on bone marrow with LGL phenotype (demonstrated on immunophenotyping at the end of 2011) with suggestive clinical features [2, 3].

Since our patient presented with severe neutropenia (ANC < 500 cells/mm³), he had clinical indication to start immunosuppressive treatment. Other treatment indications are moderate neutropenia with recurrent infections, symptomatic anaemia that is transfusion-dependent (or not) and associated autoimmune conditions requiring treatment, such as pure red cell aplasia, rheumatoid arthritis and systemic lupus erythematosus (Table 2).

Table 1: Indications to initiate immune suppressive therapy on LGLL patients. At least 1 is indicative to start treatment.

Indications for treatment initiation of LGLL	
1.	Severe neutropenia (ANC < 500 cells/mm ³)
2.	Moderate neutropenia (ANC > 500 cells/mm ³) with recurrent infections
3.	Symptomatic anaemia (transfusion-dependent or nor)
4.	Associated autoimmune conditions that require therapy (most frequently rheumatoid arthritis)

Table 2: ACR traditional classification criteria of GPA, formerly called Wegener's Granulomatosis. It states that a patient shall be considered having GPA if at least 2 of the 4 criteria are met (1990).

ACR traditional classification criteria of GPA (1990)	
Criterion	Definition
1. Nasal or oral inflammation	Presence of painful or painless oral ulcers and/or purulent or bloody nasal discharge
2. Abnormal chest radiograph	Chest radiograph (or other imaging method) that reveals nodules, fixed infiltrates and/or cavities on pulmonary parenchyma
3. Urinary sediment	Abnormal urinary sediment with microhaematuria (> 5 red blood cells per high power field) and/or red cell casts
4. Granulomatous inflammation on biopsy	Biopsy showing histopathological evidence of granulomatous inflammation within an artery wall, a perivascular area and/or an extravascular area

Although some patients may remain asymptomatic for long periods of time or have an indolent clinical course, except for a small proportion with aggressive disease (primarily those with aggressive NK-cell LGLL), most of them will eventually need drug therapy. Treatment is based on immune suppression against LGL-mediated immune response mainly through MTX, CYC or Cyclosporine A (CyA) mono therapy [3]. Because the data regarding the disease are scarce and there are no large prospective clinical trials comparing different therapeutic approaches (since it is a rare disease with few cases), there is no standard treatment neither preference amongst the immunosuppressive agents referred. Because of that, we followed recommendations from the author of the “How I Treat” journal regarding LGLL [2].

We started with MTX therapy since it is recommended for patients with neutropenia and/or rheumatoid arthritis. We also prescribed prednisone as an adjunctive treatment aiming to accelerate haematologic improvement in neutrophil count. After 6 months, patient had partial response with raise in ANC but did not had complete normalization of his blood counts. Seeking better results, we switched therapy to CYC, since CyA is used preferentially in patients with anaemia or pure red cell aplasia [2]. After another 6 months, patient’s response was reassessed and he presented with disease progression (worsening of neutropenia and development of lymphocytosis), even though a high proportion of patients respond to CYC therapy after MTX failure [3].

Considering this atypical clinical outcome of treatment failure, we conducted another immunophenotyping from the patient’s bone marrow aspirate to confirm his diagnosis in order to apply the best therapy directed towards the underlying cause before switching his medication. The result was, once again, a lymphocytic proliferation with a phenotype suggestive of LGLL. We continued to follow the “How I Treat” recommendations and tried a second-line therapy with the purine analog cladribine. They show promising results, even though there is very limited experience with them, and patients undergo a maximum of 1-3 courses due to its toxicity [2, 3]. Our patient underwent only 1 cycle of cladribine with partial response and relapse after 3 weeks. Aiming to improve his neutropenia and lymphocytosis, he returned to prednisone therapy alongside weekly G-CSF. Patient then had partial response with improvement in ANC and lymphocytosis. Since his response was sustained with this approach, we decided to not expose him to another cycle of cladribine to avoid toxicity, except in case he presented worsening of the blood counts, which he did not. Due to previous failed or unsatisfactory treatment results and considering that this time his ANC was acceptable in this particular clinical context, we maintained this therapy of prednisone alongside weekly G-CSF, albeit the outcome provided by it would be considered a partial response. This therapeutic approach was maintained with a reasonably stable course for over 3 years.

6.2. Granulomatosis with Polyangiitis (GPA)

In 2016 our patient began to exhibit symptoms suggestive of an alternative diagnosis. He developed skin lesions on the axillary region characterized as small erythematous papules and pustules (Figure 1). That context in addition to the previous multiple therapeutic failures or unsatisfactory results prompted us to reinvestigate his diagnosis. Laboratory testing revealed neutropenia persistency and leukopenia, probably due to chronic immunosuppressive therapy, as well as a c-ANCA positivity amongst other results. A new immunophenotyping by flow cytometry was conducted in 2017, and the V β TCR gene repertoire analysis revealed no evidence of clonality on the T-cell expansion, which is the underlying pathogenic process of LGLL, but rather a polyclonal LGL proliferation [3]. That made clear to us that LGLL was not his true diagnosis. In this context of uncertain diagnosis, the c-ANCA positivity triggered us to consider GPA as a possible underlying cause.

GPA, formerly called Wegener’s Granulomatosis due to a shift from eponym use to a disease-descriptive nomenclature, is an autoimmune vasculitis associated with ANCA that can cause granulomatous inflammation and glomerulonephritis and that integrates the group of ANCA-Associated Vasculitis (AAV) alongside Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) [5, 6]. According to the 2012 Chapel Hill Consensus Conference (CHCC), these AAV are characterized by necrotising vasculitis predominantly of the small to medium sized vessels with an absence or paucity of immune deposits [7].

It’s a rare disease, with an annual incidence ranging from 5-20 cases/million inhabitants and being more frequent amongst the elderly around the 6th and 7th decade, which interestingly counteracts with the younger age of our patient [6, 8, 9]. Moreover, it is more commonly seen in Caucasians and seldomly diagnosed in black people, with an increase in incidence towards the northern hemisphere, mainly in the northern Europe. This low annual incidence and scarcity of cases hampers research regarding the exact biological mechanisms underlying the pathogenesis of the disease. Because of that, its aetiology is still under debate, though it’s thought to be due an interplay between genetic factors and environmental aspects that can act as triggers for disease onset, such as recurrent infections or chronic silica exposure [8,9].

These recurrent infections can induce an inflammatory response that may give rise to an abundance of T helper cells and self-reactive B cells, the latter secreting ANCA, which it’s well-known to play a major role on the pathogenesis of GPA and other AAV [6]. These ANCA auto antibodies binds to the PR3 and MPO exposed on the surface of neutrophils primed by cytokines released during the triggering infection, leading to the de granulation of these ANCA-linked neutrophils [6, 8]. This de granulation process discharges reactive oxygen species, proteolytic enzymes and cytokines

that promote damage to the blood vessels, mainly the small-sized ones, which may explain the disease's frequent pulmonary and renal manifestations, since these regions are capillary rich, making them a likely target.

This molecular scenario of immune response implicates an elevated CRP and ESR on laboratory results, which were present during patient presentation and diagnosis reinvestigation. It also prompts ANCA detection through IF, which can reveal a cytoplasmic staining pattern called c-ANCA, associated with PR3 binding, or a perinuclear one called p-ANCA, associated with MPO binding, as well as MPO and PR3 autoantibody detection [6, 8]. Despite the c-ANCA positivity during patient's diagnosis reinvestigation, enzymatic fluoroimmunoassay revealed an absence of PR3 and MPO autoantibody. This apparent contradictory result between a positive c-ANCA and a negative PR3 is further explained by the fact that our patient's previous immunomodulatory treatment conducted since 2012 may be held responsible for the reduction in PR3 antibody positivity [8].

Although skin lesions are frequent manifestations of GPA (present in up to 50% of cases), they are neither specific nor pathognomonic for the disease, and those presented by the patient in 2016 were, at first glance, unlikely due to GPA [6, 9]. The most frequent dermatological manifestation in GPA is purpura that can be ulcerating and/or necrotic and is primarily located in the lower limbs [9, 10]. This contrasts with our patient's presentation, who had erythematous papules and pustules similar to herpes lesions in the upper region of the body. Due to this atypical presentation unlikely related to vasculitis, our clinical reasoning initially was not inclined to consider GPA as a possible aetiology, but was later on accounted to it due to its highly variable clinical presentation, thus making it a possible, though rare, manifestation [10].

Moreover, in 2019 our patient attended the emergency medical care with a clinical presentation suggestive of pneumonitis. He was admitted to the facility aiming treatment and medical investigation, which revealed through laboratory testing a normal renal function, an inflammatory state with elevated CRP and a very high titre of atypical c-ANCA on IF with a still negative PR3 antibody result. The computed tomography conducted after his stabilization revealed a few pulmonary calcifications in the parenchyma and prompted us thinking of GPA as a possible diagnosis, since pulmonary manifestations such as these - alongside alveolar hemorrhage, cough and dyspnoea - can occur in 50-90% of cases [6, 9]. Not only that, but also a head computed tomography revealed mucosal thickening of the sinus, suggestive of rhino sinusitis, which added more likelihood that GPA was his true diagnosis, since ear, nose and upper airway manifestations - which include rhino sinusitis - are common and can be reported in about 90-100% of patients [6, 8].

These upper and lower airway manifestations may have flared due

to patient's pneumonitis, which could possibly have been an infectious trigger for disease pathogenic onset. Although frequent in 40-100% of cases, renal manifestations - often pauci-immune crescentic necrotizing glomerulonephritis - were absent during our patient's clinical course, as confirmed by his normal blood urea, serum creatinine and eGFR [9]. Nonetheless, it is important to keep track on renal function, since GPA patients can die due to rapidly escalating renal failure with uraemia if left untreated and have their prognosis affected depending on initial eGFR [8, 9].

Constitutional symptoms, such as those presented by the patient in late 2011, are common in GPA's initial clinical course, being estimated to occur in about 50% of cases at disease onset [8, 9]. However, the fever and malaise reported in the beginning of the disease, alongside the neutropenia revealed at the time, were accounted not due to the GPA, but to his former diagnosis of LGLL, or more appropriately his LGL proliferation secondary to GPA.

Regularly, after these laboratory and clinical signs and symptoms suggestive of GPA, a biopsy from the lung lesions would have been conducted after their localization to confirm the disease's diagnosis through a histopathological study [8]. Though recommended, the biopsy was not taken due to the small size of the lesions and to the possibility of making the diagnosis without this invasive procedure. That is due to the American College of Rheumatology (ACR) traditional classification criteria, which classifies a vasculitis patient as having GPA if he presents at least 2 of the 4 criteria listed (Table 2) [11]. Since our patient had nasal inflammation, reflected through his rhino sinusitis, and abnormal chest imaging, he was classified as having GPA, sparing him from a more invasive diagnostic approach.

With his new diagnosis of GPA established in 2020, patient began drug therapy with MTX. It is well-known that modern treatment switched disease's characteristic from life-threatening to chronic, but with a relapse rate of 50% within 5 years of treatment [8, 9]. The treatment is consisted of a first phase that aims induction of remission (based upon the combination of corticosteroids and another immunosuppressive medication), that lasts around 3-6 months, and a second phase aimed at maintaining remission and avoiding relapse [6, 8, 9]. The standard drug therapy chosen for the remission induction phase is prednisolone combined with CYC, the latter being oral or intravenous [12]. Although this approach leads to remission in 90% of patients, it is highly associated with adverse effects due to drug toxicity, such as bone marrow suppression, haemorrhagic cystitis, bladder cancer and infertility [6, 12].

In order to avoid these negative side effects, alternative therapies can be employed in certain situations. This is the case for MTX, that can be used in mild to moderate cases in early disease as a less toxic agent [6, 8, 9]. A trial conducted by Kirsten de Groot et al. revealed that MTX is non-inferior to CYC regarding remission induction, but it is associated with higher and earlier relapse rates

[12]. Although not associated with severe immune suppression, this drug can cause liver dysfunction, which can be circumvented by the administration of weekly folic/foinic acid [12]. Since our patient did not presented signs of renal involvement and only had sparse and small pulmonary calcifications and rhino sinusitis, MTX was chosen over CYC therapy with good clinical response.

7. Conclusion

The case presented herein represents an atypical GPA manifestation. Although later in the clinical course the patient had a more likely presentation of the disease with pulmonary and upper airway manifestations, initially it manifested as an apparent LGLL that was later discovered to be a reactive LGL polyclonal proliferation. The underlying cause for this atypical presentation is unknown, but it could be a T-cell proliferation due to an inflammatory response against the recurrent infections that could presumptively had acted as a trigger for GPA development, but there is no evidence to that. Indeed, more investigation is needed, since both GPA and LGLL are rare diseases with few cases and a scarcity of data regarding the underlying pathogenesis.

References:

1. Audemard A, Lamy T, Bareau B, Sicre F, Suarez F, Truquet F et al. Vasculitis associated with large granular lymphocyte (LGL) leukemia: Presentation and treatment outcomes of 11 cases. *Seminars in Arthritis and Rheumatism*. 2013; 43:362-6.
2. Lamy T, Loughran TP. How I treat LGL leukemia. *Blood*. 2011; 117:2764-74.
3. Lamy T, Moignet A, Loughran TP. LGL leukemia: from pathogenesis to treatment. *Blood*. 2017; 129:1082-94.
4. Lamy T, Loughran TP. Current concepts: large granular lymphocyte leukemia. *Blood Reviews*. 1999; 13: 230-40.
5. Falk RJ, Gross WL, Guillevin L, Hoffman GS, Jayne DRW, Jennette JC et al. Granulomatosis with Polyangiitis (Wegener's): An alternative name for Wegener's Granulomatosis. *Arthritis & Rheumatism*. 2011; 63: 863-4.
6. Lutalo PM.K, D'Cruz DP. Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). *Journal of Autoimmunity*. 2014; 94-8.
7. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis & Rheumatism*. 2012; 65: 1-11.
8. Berden A, Goceroğlu A, Jayne D, Luqmani R, Rasmussen N, Bruijn JA et al. Diagnosis and management of ANCA associated vasculitis. *BMJ*. 2012; 344: e26–e26.
9. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): Clinical aspects and treatment. *Autoimmunity Reviews*. 2014; 13: 1121-5.
10. Francès C. Wegener's Granulomatosis. *Archives of Dermatology*. 1994; 130: 861.
11. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis & Rheumatism*. 2010; 33: 1101-7.
12. De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis & Rheumatism*. 2005; 52: 2461-9.