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Case Report

A Lady with Multiple Cavitating Lung Nodules

Sunil Kumar[1], Mahismita Patro[1], Ramesh Singh Pal[1], Dipti Gothi[2]* and Anshul Jain[1]

[1]*Department of Pulmonary Medicine, ESI-PGIMSR, Basaidarapur, New Delhi, India*

[2]*Professor, Department of Pulmonary Medicine ESI-PGIMSR, Basaidarapur, New Delhi, Guru Gobind Singh Indraprastha University, Delhi, India*

***Corresponding Author:** Dipti Gothi, Professor, Department of Pulmonary Medicine ESI-PGIMSR, Basaidarapur, New Delhi, Guru Gobind Singh Indraprastha University, Delhi, India.

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Abstract

The granulomatosis with polyangitis (GPA) is an under-diagnosed disease. If untreated leads to death in 82% of patients in 1 year. Thus, it is important to recognize the disease early as effective therapy improves patient survival. We report a 58 years lady with joint pain since 18 months, nasal discharge since 10 months, fever since 9 months and oral ulcer since 1 month. The blood investigations revealed anemia, renal dysfunction, albuminuria and C-ANCA positivity. The imaging studies showed multiple cavitating lung nodules and ethmoidal sinusitis suggesting a diagnosis of systemic GPA based on the 2017 American college of rheumatology (ACR)/European Medicine Agency Algorithm (EMA) criteria for early diagnosis of GPA. The remission induction was done with prednisolone with pulse cyclophosphamide. The remission maintenance was done with prednisolone and mycophenolate mofetil. This case highlights the importance of early diagnosis and appropriate treatment of GPA that leads to complete recovery.

Keywords: *Multiple Cavitating; Lung Nodules*

Case Report

A 58 year old lady, never smoker, home-maker presented with multiple joint pain for 18 months, nasal discharge for 10 months, low grade fever for 9 months and oral ulcer for 1 month. She had involvement of multiple small and large joints without any swelling, tenderness or morning stiffness. There were no specific respiratory complaints. She was a known diabetic for which she was on irregular treatment. Her earlier records revealed history of intermittent sinusitis. She had received empirical anti-tubercular treatment (ATT) for the last 6 months from outside based on the chest radiograph findings though her sputum for acid fast bacilli was negative. There was no clinical improvement on ATT. There were no other comorbidities. On physical examination, she was conscious and oriented with a pulse rate of 80 per min, blood pressure of 116/76 mmHg, respiratory rate of 18 per min and oxygen saturation of 98% on room air. The general examination revealed presence of pallor. There was absence of cyanosis, clubbing, peripheral lymphadenopathy and pedal edema. The upper respiratory tract examination showed presence of reddish oral ulcers over tongue and palate, deviated nasal septum to left side and nasal septal hypertrophy. The lower respiratory system examination revealed bilateral normal vesicular breath sounds. The other systemic examination was normal.

The routine biochemical and hematological investigations were done which showed hemoglobin of 8.7g/dl and total leucocyte count of 9200/cu mm. The serum urea was 57 mg/dl and creatinine was 2.5 mg/dl. The random blood sugar level was 220 mg/dl. The urine routine and microscopic examination showed presence of albumin 2+. The serum rheumatoid factor and antinuclear antibody level was normal. Her chest radiograph done 6 months back during tuberculosis diagnosis and at presentation are shown in figure 1. They showed multiple nodular lesions with a few of them showing cavitation in both the lung fields. There was progression of lesions over 6 months. The high resolution computed tomography (CT) scan of the chest revealed bilateral cavitating lung nodules (Figure 2). The non-contrast CT of the paranasal sinuses suggested minimal left ethmoidal sinusitis with nasal septal deviation towards left side (Figure 3). The sputum examination for acid fast bacilli smear, gram stain and bacterial culture was negative. She underwent fibre-optic bronchoscopy which was

normal. The bronchoalveolar lavage fluid cytology, acid fast bacilli smear, gram stain and bacterial culture, fungal stain and fungal culture were also normal. The qualitative assay for cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) by the immunofluorescence assay (IFA) was positive. The perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) and anti-glomerular basement membrane antibodies (anti- GBM) were negative.

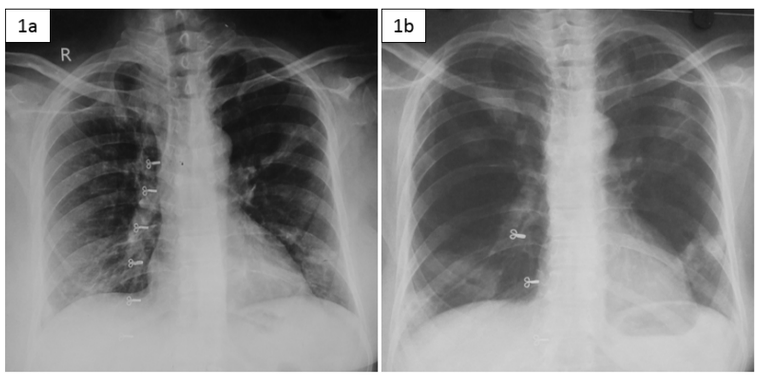

Figure 1

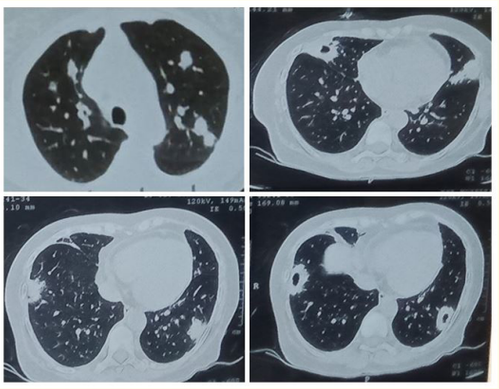

Figure 2

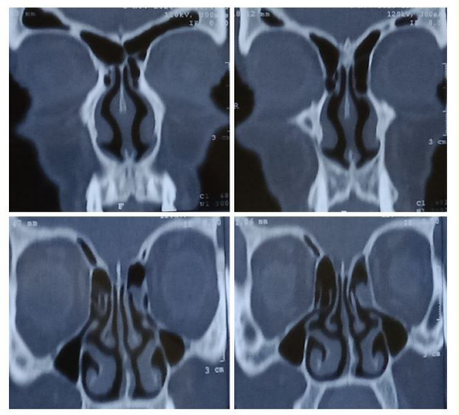

Figure 3

Task 1

Which of the following is the most likely diagnosis?

a. Pulmonary tuberculosis

b. ANCA associated vasculitis (AAV)

c. Fungal infection

d. Lymphoma.

Answer- b. ANCA associated vasculitis (AAV)

The differentials for multiple cavitating lung nodules are given in table 1. The infectious diseases such as tuberculosis and fungal infections are commonest. The non-infectious causes include primary or metastatic lung malignancies, granulomatosis with polyangitis (GPA), pulmonary lymphoma etc [1]. In our patient since the repeated microbiological investigations were normal and there was a lack of clinical response to ATT, tuberculosis and fungal infection were ruled out. There were no peripheral or mediastinal lymphadenopathy and the bronchoalveloar lavage fluid malignant cytology was also negative thus lymphoma was less likely. The multisystemic involvement of lung, kidney, upper respiratory tract along with the presence of polyarthralgia and anemia suggested the presence of a systemic disease such as small vessel vasculitis. Also the C-ANCA was positive, thus AAV was the most likely diagnosis.

Infectious Causes	Non-Infectious Causes
Tuberculosis	Granulomatosis with polyangitis
Bacterial infections	Metastases
Fungal infections	Bronchogenic carcinoma
Septic emboli	Pulmonary lymphoma
Nocardiosis	Sarcoidosis
Paragonimiasis	Pulmonary Langerhans cell histiocytosis
Echinococcosis	Pulmonary embolism
	Lymphomatoid granulomatosis
	Pneumoconiosis

Table 1: *Causes of multiple cavitating lung nodules.*

Task 2

Which AAV the patient is likely to have?

a. Eosinophilic granulomatosis with polyangitis (EGPA)

b. Systemic granulomatosis with polyangitis (GPA)

c. Limited GPA

d. Microscopic polyangitis (MPA)

Answer- b. Systemic granulomatosis with polyangitis (GPA).

The AAV is a broad category of small vessel vasculitis associated with ANCA positivity. It includes GPA, EGPA and MPA [2,3]. The ANCA are a group of autoantibodies directed against the target antigens proteinase 3 (PR3) or myeloperoxidase (MPO) located in the leucocytes. The ANCA can be detected by the IFA or the enzyme linked immunosorbent assay (ELISA). The IFA has high sensitivity whereas the ELISA has high specificity for the detection of ANCA. The immunofluorescence-staining pattern decides if the patient has C-ANCA or P-ANCA positivity. If the staining pattern is perinuclear it denoted as P-ANCA and the antibodies are directed against MPO. If the staining pattern is diffuse though-out the cytoplasm it is denoted as C-ANCA and it is due to PR3 antibodies [4].

The GPA is frequently associated with ANCA positivity. In about 90% of cases of GPA, the ANCA is C-ANCA. About 30 - 50% of the EGPA and MPA are associated with P-ANCA [5]. All the AAVs commonly have lung and kidney involvement and thus are the frequent causes of pulmonary renal syndrome. The EGPA has a different presentation and is classically characterized by presence of asthma, peripheral eosinophilia and vasculitis. It may have associated sinusitis, mononeuritis multiplex and fleeting opacities on the chest radiograph. The MPA and GPA have similar manifestations with nonspecific systemic symptoms as fever, polyarthralgia, weight loss, malaise. Thus they are likely to be frequently mis-diagnosed as infections or malignancies.

The GPA is a systemic necrotizing small vessel vasculitis with multi-systemic granulomatous inflammation. It was previously known as Wegener's granulomatosis, which has been changed to GPA in January 2011 [6]. The GPA is characterized by classical clinical triad of ear, nose and throat (ENT), lung and kidney involvement. The 2017 American college of rheumatology (ACR)/European Medicine Agency Algorithm (EMA) revised criteria for the early diagnosis of GPA are given in table 2. The diagnosis requires presence of entry criteria with at least 4 points. It is classified as limited GPA when the score is 4 and systemic GPA when the score is 5 along with kidney involvement [7].

Organ Involvement	**Score in Points**
ENT involvement	**Up to 4 points**
• Bloody nasal discharge/crusting/ulcer/ severe nasal pain	1
• Oral necrotic ulcer	1
• Strawberry gum hyperplasia	2 (total upto 2 points for oral cavity).
• Sinusitis	1
• Bilateral otitis media or otitis media with sensory-neural hearing loss	1
• Proptosis	2
• Saddle-nose deformity	2
• Subglottic stenosis	2
• Sinonasal destruction	2
• Mastoiditis	1

Lung involvement
• Hemoptysis:
• Radiology: Nodule
  • Cavity
  • Fixed infiltration
	Up to 2 points
	1
	2
	2
	1

Kidney involvement • Hematuria or proteinuria or RBC cast	**1 point**
ANCA positivity • Positive P-ANCA • Positive C-ANCA	**Up to 2 points** 1 2
Biopsy finding • Small vessel vasculitis without eosinophilia • Granulomatous inflammation without eosinophilia	**Up to 2 points** 1 2
Entry criteria: No other possible explanation/diagnosis for the condition **Diagnosis: Limited GPA**: ENT and/or lung involvement: score ≥4/11 **Systemic GPA**: ENT and/or lung with kidney involvement: score ≥ 5/11.	

Table 2: *2017 ACR/EMA revised criteria for early diagnosis of GPA.*

In our patient the ENT involvement in form of oral ulcer, deviated nasal septum and nasal septal hypertrophy constituted 3 points, lung involvement in form of bilateral cavitating lesions constituted 2 points and presence of albuminuria suggested kidney involvement and score of 1. The presence of C-ANCA positivity added the total score to 8. Thus she was diagnosed as systemic GPA.

Task 3

Is lung biopsy indicated for the confirmatory diagnosis of GPA in this case?

a. Yes

a. No

Answer- b. No

The patient satisfied the 2017 ACR/EMA diagnostic criteria for systemic GPA based on non-invasive evaluation (Score 8 out of 11). So, invasive lung biopsy was not required as it would not affect the disease management. The lung biopsy is not required routinely for the diagnosis of GPA. The biopsy is required for ruling out some other diagnosis and for further evaluation of patients suspected of having relapsing GPA. The lung biopsies vary in their diagnostic sensitivity. Transbronchial biopsies are positive in only 12% of GPA [8]. The open lung biopsies provide a higher diagnostic yield but they are more invasive [9]. The CT or ultrasound guided biopsy may be considered in large lung nodules abutting the chest wall.

Task 4

Which of the following questionnaires is used to assess disease activity in GPA?

a. SOFA

b. BVAS

c. PESI

d. GSAQ

Answer- b. BVAS

GPA and all other AAVs are assessed with the BVAS score (Birmingham vasculitis activity score). It is the most studied and widely used criteria for assessing disease activity. The BVAS score is based on symptoms and signs of nine separate organ systems: general, cutaneous, ENT, mucous membranes, respiratory, cardiovascular, abdominal, renal and nervous system (Table 3). The disease features are scored if they are attributable to active vasculitis. The BVAS score can be computed easily using the online calculators. This score can be used to compare disease activity between patients on different treatment regimens and to measure the response to treatment in an individual patient [10]. According to the BVAS score, remission is defined as an absence of BVAS items for a sustained period from 2 to 6 months. There might be a few elements of the BVAS score persistent due to irreversible injury induced during the active disease. The relapse is defined as recurrence of BVAS items. The response is defined as ≥ 50% reduction in the initial BVAS score. The BVAS score is more sensitive and specific than biochemical measurement for reflecting disease activity [10].

Organ System Involved	
1. General-	6. Cardiovascular
Myalgia	Loss of pulses
Arthralgia / arthritis	Pericarditis
Fever ≥38° C	Ischaemic cardiac pain
Weight loss ≥2 kg	Cardiomyopathy
	Congestive cardiac failure

2. Cutaneous- Purpura, ulcer Gangrene Other skin vasculitis	7. Abdominal- Peritonitis Bloody diarrhoea Ischaemic abdominal pain
3. Mucous membranes / eyes Mouth ulcers Significant proptosis Scleritis/ Episcleritis Conjunctivitis / Blepharitis / Keratitis Retinal changes	8. Renal Hypertension Proteinuria >1+ Hematuria ≥10 RBCs/hpf Serum creatinine 125-249 µmol/L* Serum creatinine 250-499 µmol/L* Serum creatinine ≥500 µmol/L* Rise in serum creatinine>30% or fall in creatinine clearance >25%
4. ENT Bloody nasal discharge / crusts / ulcers / granulomata Paranasal sinus involvement Subglottic stenosis	9. Nervous system Headache, Meningitis ,Organic confusion Seizures (not hypertensive) Cerebrovascular accident Mononeuritis multiplex
5. Chest Wheeze Nodules or cavities Endobronchial involvement Massive haemoptysis / alveolar Hemorrhage Respiratory failure	10. Other
Total score ……The presence of any manifestation related to active vasculitis is scored 1. If all the abnormalities are deemed to be not new or worse in the prior 4 weeks, it is labeled as persistent disease.	

Table 3: *Birmingham Vasculitis Activity Score (BVAS) for assessment of disease activity in GPA.*

The SOFA score (sequential organ failure assessment score) was created by the European society of intensive care medicine. It provides prognostic information on in-hospital survival in patients of severe sepsis [11]. The PESI score (pulmonary embolism severity score) is used for risk stratification of patients with acute pulmonary embolism which is mandatory to determine the appropriate therapeutic approach [12]. The GSAQ score (global sleep assessment questionnaire) is used for screening of sleep disorders [13].

Task 5

Which of the following drugs cannot be used for induction of remission in our case?

a. Cyclophosphamide

b. Glucocorticoids

c. Rituximab

d. Methotrexate.

Answer- d. methotrexate

The mainstay of treatment for active GPA includes immunosuppressive therapy. The choice of drugs is based on the activity and the severity of disease. An active disease is defined as the presence of new, persistent, or worsening clinical signs and/or symptoms attributed to GPA that are not related to prior damage. The severity is assessed by the presence of organ threatening or life threatening disease. The presence of renal involvement in form of active glomerulonephritis, lung involvement in form of pulmonary hemorrhage, cerebral vasculitis, progressive peripheral or cranial neuropathy, orbital pseudotumor, scleritis, gastrointestinal bleeding and cardiac disease due to vasculitis such as pericarditis, myocarditis etc are considered as organ threatening or life-threatening disease. The patients with a non-organ or non-life-threatening disease have no such manifestations and are considered as non-severe disease. They may have rhinosinusitis, arthritis or pulmonary nodules [14]. Our patient had pulmonary nodules but also renal involvement in form of active glomerulonephritis, hence it was labeled as active, severe GPA. There are 2 phases of treatment: remission induction phase and remission maintenance phase. The remission induction phase requires treatment with combination of glucocorticoids and an immunosuppressant. The standard or high dose glucocorticoid regimen used for remission induction is oral prednisolone at a dose of 1mg/kg/day (maximum 80 mg). The patients who are severely ill may be given pulse methylprednisolone therapy i.e. 1000mg intravenous daily pulses for 3 days initially followed by oral prednisolone. The recent guidelines have however conditionally recommended reduced-dose glucocorticoid regimen over a standard-dose glucocorticoid regimen for remission induction. Reduced dose glucocorticoid regimen starting with pulse methylprednisolone with 1 week of high dose oral glucocorticoids and then rapid tapering has been successfully evaluated [15]. The drugs of choice for the induction of remission of active, severe GPA are steroid along with cyclophosphamide or rituximab [14,16]. The pulse intravenous cyclophosphamide regimen is associated with a theoretical lower risk of toxicity due to lower cumulative dose compared to oral dosing. Cyclophosphamide based regimen has long been preferred as initial therapy in patients presenting with more severe kidney disease or pulmonary hemorrhage. However cyclophosphamide is associated with major adverse effects such as bone marrow suppression, infertility and alopecia. The recent Rituximab for ANCA-Associated Vasculitis (RAVE) trial and the Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) trial have found rituximab to be as effective as cyclophosphamide for the induction of remission in AAV [17,18]. Thus the recent 2021 ACR/Vasculitis Foundation Guideline for the management of GPAs prefers rituximab over cyclophosphamide since rituximab is considered less toxic than cyclophosphamide. Rituximab may be associated with hypogammaglobulinemia as a significant side effect. Hence serum immunoglobulin levels should be done prior to each course of rituximab and in patients with recurrent infections [19].

The induction of remission in non-severe GPA should be done with a combination of glucocorticoids and immunosuppressant. The recommended immunosuppressant for non-severe disease is methotrexate. Other agents that can be used are rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil [14]. Methotrexate is preferred for non-severe GPA due to greater evidence and clinical experience with methotrexate in this group and lesser toxicity compared to cyclophosphamide. The trials comparing methotrexate versus cyclophosphamide for remission induction showed that methotrexate had less effective disease control on the long term follow up. Hence methotrexate should be considered only for non-severe disease.[20] Since our patient had severe GPA in form of active glomerulonephritis, methotrexate cannot be used for remission induction in her.

Once the remission has been achieved, remission maintenance phase of treatment should be started. The maintenance therapy for severe and non-severe disease is the same. The maintenance phase of GPA treatment requires a combination of low dose glucocorticoids (prednisolone tapered to 5 - 10 mg daily) and an immunosuppressant. The other immunosuppressant along with steroid depends on which drug was used for the remission induction. If rituximab or cyclophosphamide were used for induction the order of preference for maintenance are rituximab, methotrexate, azathioprine or mycophenolate mofetil or leflunomide. If remission was induced with methotrexate, azathioprine or mycophenolate mofetil, the same medication should be continued for remission maintenance. The choice of immunosuppressant should be based on the disease severity and patient related factors. The optimal duration of maintenance therapy is not exactly defined but recommended for at least 18 months and further guided by patient's clinical condition [14].

Our patient was started on remission induction therapy with oral prednisolone 1 mg/kg/day and intravenous pulse cyclophosphamide. The cyclophosphamide pulses were given every 2 weeks for first 3 doses and then every 3 weeks for next 3 doses. The BVAS score at time of diagnosis of GPA was 18 which reduced to 5 with residual kidney disease after completion of 6 cycles of pulse cyclophosphamide therapy. As there was > 50% reduction in the initial BVAS score, our patient was responsive to treatment. Her follow up chest radiograph and high resolution CT scan of the chest done after 3 months showed resolution of the lung lesions (Figure 4). The patient was switched to remission maintenance therapy with prednisolone (tapered to a dose of 10mg daily) and mycophenolate mofetil, which will be continued at least for 18 months.

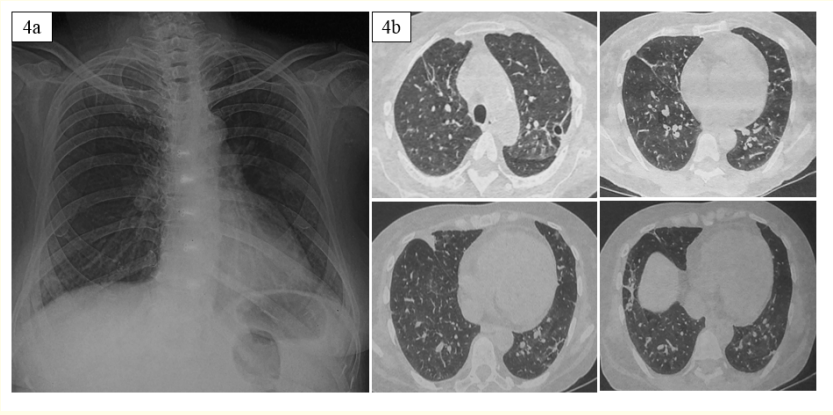

Figure 4

Discussion

The prevalence of GPA is about 3 in 100,000. The peak age at onset in GPA is fourth and fifth decade but 15% of cases have the age at onset less than 19. The early diagnosis of GPA and early treatment can result in a complete remission. The delay from onset to the time of diagnosis in GPA ranges from 2 to 20 months [21]. Sinusitis is the most common initial presentation seen in 70% of cases. The presence of chronic rhinosinusitis is the classical ENT finding in this disease [22].

There have been three criteria for the diagnosis of GPA: the 1990 ACR classification criteria [23], the EMA diagnostic criteria [24] and the Iran criteria for early diagnosis of GPA [25]. Recently the Iran criteria have been modified a little and a new criteria is advocated by Iraj Salehi-Abari known as the 2017 ACR/EMA revised criteria [7]. The 2017 ACR/EMA revised criteria help in establishing the diagnosis of GPA earlier with a lag period of a few weeks only. An accurate and cost-effective diagnosis of GPA requires a four step practical approach. One must go through the steps one by one till the diagnostic criteria are satisfied [7]. The first step involves detailed history and physical examination, routine blood investigations including complete blood count, renal and liver function test, urinary analysis and ANCA serology. The chest radiograph and radiograph of paranasal sinuses should also be performed. The second step should approach towards CT scan of sinuses and lungs. The third step is to examine the ENT tract via endoscopy and sinus biopsy. The final step considers biopsy of other sites such as skin, kidneys or lungs. In our patient the diagnosis was achieved at the 2nd step only, thereby averting the need for biopsy.

The treatment of GPA involves combination of glucocorticoids and immunosuppressants. The various drugs along with their dosing regimens have been summmarised in table 4. The GPA is characteristically a relapsing disease and has a long-term lifestyle consequences. The management of relapse involves reintroduction of the induction phase. The GPA when untreated leads to a fatal course resulting in death of 82% of patients within 1 year. The early and appropriate treatment results in remission in more than 90% of the patients. The prognosis is worse when the kidneys are involved [26]. Hence it is of paramount importance to recognize the disease early in its limited form, as effective therapy would improve the patient survival. A 'holistic' approach to treatment and ongoing care should be adopted. The patients with GPA should be given a clear verbal explanation of the nature of their disease, the treatment options, the side effects of treatment, and the short-term and long-term prognosis.

Conclusion

The diagnosis of GPA should be considered in any case of bilateral cavitating lung nodules. The GPA is classically characterised by involvement of ENT, lung and kidney. The 2017 ACR/EMA revised criteria help in early diagnosis of GPA. The disease activity and treatment response is assessed using the BVAS score. The correct diagnosis and early treatment of GPA would reduce the morbidity and mortality.

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