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Title:

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Date:

2021-03-01

Citation:

Paxton, L., Champion De Crespigny, P. & Nicholls, K. (2021). Granulomatosis with polyangiitis complicated by genital involvement: sustained response to rituximab. Internal Medicine Journal, 51 (3), pp.444-445. <https://doi.org/10.1111/imj.15224>.

Persistent Link:

<https://hdl.handle.net/11343/298282>

## **Granulomatosis with Polyangiitis complicated by Genital Involvement: Sustained response to Rituximab**

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A 25-year-old woman presented with 24 hours of pleuritic pain and small volume haemoptysis, following lethargy and dry cough for two weeks. Frequent episodes of sinusitis had been treated with antibiotics over the previous three years.

CXR revealed multiple cavitating lesions and peripheral nodules. Serum creatinine was normal, but mid-stream urine contained 300,000 glomerular red blood cells (RBCs), 20,000 leukocytes, and hyaline and RBC casts. Anti-neutrophil cytoplasmic antibody (PR3) was positive. Renal biopsy showed focal necrotising glomerulonephritis with focal sclerosis and cellular crescents in 3/18 viable glomeruli, consistent with granulomatosis with polyangiitis (GPA). She responded well to initial treatment with prednisolone and co-trimoxazole.

Two years later, relapse was characterised by recurrent sinusitis and haematuria, prompting recommencement of high dose prednisolone and cotrimoxazole, again with good response. Symptomatic recurrence (relapse 2) followed steroid cessation one year later, and azathioprine was added. The patient then presented (relapse 3) with new offensive cervical discharge and per vaginal bleeding. Gynaecological examination revealed a large irregular cervical ectropion with vaginal wall extension. Papanicolaou test was negative and biopsy showed extensive ulceration, necrosis and inflammation in cervix and posterior vaginal wall, clusters of multinucleate giant cells and vasculitis. High-dose prednisolone gave good response, but with steroid dose reduction pulmonary and sinus disease recurred (relapse 4), resistant to cyclophosphamide, mycophenolate and further corticosteroid. Biopsy confirmed relapse of disease in her cervix, and ear drum rupture plus new lesions on chest CT (relapse 5) prompted a therapeutic trial of single-dose, off-label compassionate rituximab (375mg/m<sup>2</sup>). Total remission was achieved, and the cervical disease has not recurred. Pulmonary and sinus disease relapsed eight months post rituximab, but re-dosing six monthly for two years subsequently maintained remission.

A seventh relapse was suspected at 6 months after her fifth dose of rituximab, when she presented with new fatigue, dyspnoea and tachycardia. A further dose of rituximab was given, but investigations

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.15224](https://doi.org/10.1111/imj.15224)

however were typical of Grave's Disease and negative for active GPA. All clinical and biochemical abnormalities serendipitously responded completely and rapidly to rituximab.

Fifteen years later, she remains well, in complete clinical and serological remission.

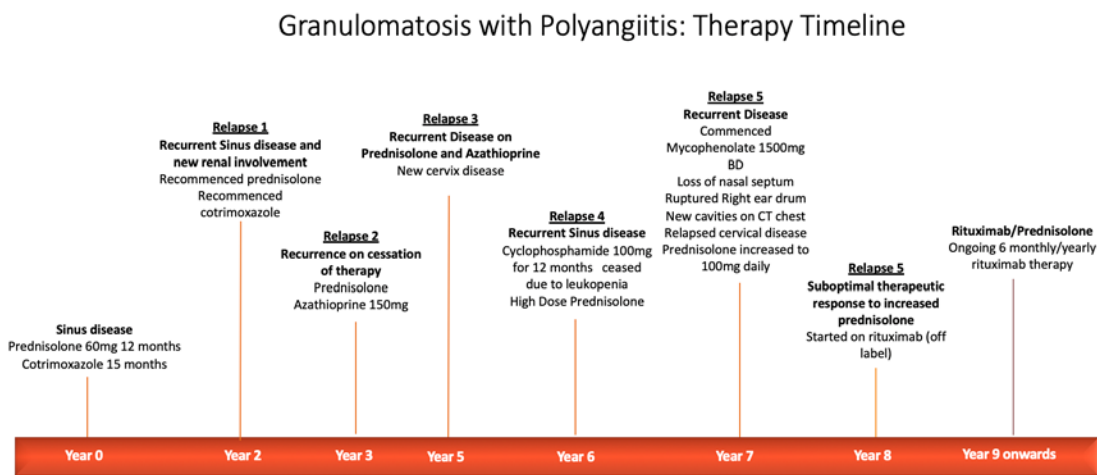


Figure 1. Granulomatosis with Polyangiitis: Therapy Timeline

DISCUSSION

Genital tract involvement in GPA whilst unusual, has been reported in the literature [1-6], with most published cases showing varying responses to cyclophosphamide. A case by Bastone et al. demonstrates near resolution of disease at twenty months post commencement of rituximab therapy.

Though similar, our case differs in treatment, with initial use of co-trimoxazole, oral rather than intravenous cyclophosphamide, and no methotrexate. Most importantly, this case demonstrates a sustained response to rituximab over fifteen years, and although rituximab is now standard therapy, its off-label use in this patient was empirical. The optimal dosing regimen remains untested.

This case illustrates the protean clinical manifestations of GPA, highlighting its varying manifestations over the disease course and the role rituximab may play in treatment of cervix disease.

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