Successful treatment of gynaecological involvement of granulomatosis with polyangiitis (Wegener's granulomatosis) by rituximab

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ABSTRACT

Granulomatosis with polyangiitis, formerly called Wegener's granulomatosis, is a disease for which the treatment options are increasing, with the recent publication of several studies concerning the use of rituximab. The disease typically involves the upper airways, lungs and kidneys, but other far less frequent localisations are possible. Here, we describe a case of isolated relapse of granulomatosis with polyangiitis affecting the uterine cervix and upper vagina which dramatically responded to rituximab therapy, after failure of methotrexate treatment. This is the first documented response to rituximab of gynaecological involvement in granulomatosis with polyangiitis.

Case report

In March 2008, at the age of thirtyone, our patient was diagnosed with granulomatosis with polyangiitis, based on migratory polyarthritis most prevalent at the knees but including fingers, wrists and shoulders to a lesser degree, biopsy-proven leucocytoclastic vasculitis, right maxillary sinusitis and appropriate serologic findings with anti-neutrophil cytoplasmic antibodies (ANCA) and anti-proteinase 3 (PR3) antibodies. A biopsy of the right maxillary sinus showed inflammation, necrosis and vasculitis, but no granuloma nor giant cell. Initial immunosuppressive treatment consisted in steroid therapy (starting daily dose of 32 mg methylprednisolone) and six intravenous pulses of cyclophosphamide 500 mg at two week's interval. Complete remission was promptly achieved and methotrexate maintenance therapy was prescribed (20 mg per week with folic acid supplements the following day).

Steroids were tapered and stopped within the year, while methotrexate therapy was progressively reduced and interrupted in January 2010.

In February 2010, she began suffering



Fig. 1. Representative microphotographs of uterine cervix showing granulomatous inflammation and vasculitis. A. A large granuloma with central necrosis and accumulation of neutrophils. Multinucleated macrophages can be seen among the epithelioid cells (arrows). B. High magnification showing multinucleated macrophages and plasma cells around dilated arterioles. C. The wall of a larger arteriole is focally inflarmatory cells. Scale bars, 100 µm.

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CASE REPORT

PET/CT Baseline



Fig. 2. Representative incidence of comparison of PET (A, D), CT (B, E) and combination imaging (C, F) showing improvement six months after rituximab therapy. The cervix may be visualised posterior of the bladder which is hypermetabolic due to urinary excretion of 18-FDG. Δ SUV= -4.78/-45%.

from metrorrhagia which progressively increased over the following months. She underwent investigations by her gynaecologist which did not lead to an explanation at that time. The bleeding significantly altered her quality of life and also had a major negative psychological impact. In March 2011, due to a new increase in the anti-PR3 antibody titers (up to 101U/mL; normal : <15), a 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan was performed. Moderate localised activity was detected in the area of the uterine cervix, which lead to a new gynaecological examination showing severe ulcerative, inflammatory lesions of the cervix and upper vagina. Conization and resection of a vaginal patch were performed. Pathological examination revealed ulcerative granulomas and vasculitis, highly indicative of granulomatosis with polyangiitis (Fig. 1). No neoplastic lesions were suggested and no mycobacteria were detected. Accordingly, treatment by methotrexate was resumed at the dose of 20 mg per week, without clinical benefit over the following months.

In October 2012, the patient was referred to our Rheumatology Department in order to discuss further treatment options. A new FDG-PET scan showed activity in the cervix and upper vagina (Fig. 2A). A new biopsy revealed inflammation and giant cells but vasculitis was not detected in the specimen, this time. In November 2012, the patient received two doses of one gram of rituximab at a fourteen-day interval, with premedication including 125 mg methylprednisolone, anti-histamines and acetaminophen. No toxic reaction was observed during either of the infusions. At her first follow-up visit in January 2013, she did not describe any significant improvement of her bleeding. Treatment was not modified at this point while we were awaiting the full effect of rituximab, which was expected to appear in the upcoming weeks. At her following visit in March 2013, she described a significant improvement in her metrorrhagias. A new FDG-PET scan was performed and showed a significant reduction in activity at the level of the uterine cervix, and a reduction in activity and spatial involvement of the vagina (Fig. 2B). At her last visit in July 2014, she presented merely intermittent post-coital bleeding of a minor volume without dyspareunia but no longer suffers from metrorrhagias.At the gynaecological examination, a small erosion persisted, as well as an anterior synechia between the vaginal mucosa and the anterior cervical lip, which could account for the remaining symptoms.

Discussion

A few cases of gynaecological involvement have already been reported in granulomatosis with polyangiitis (1-9). They are summarised in the Table. Six of the patients were menopaused at the time of presentation. The average age of patients at the time of diagnosis was of 56.6 years old. In most cases, the diagnosis was established through histological analysis of cervical biopsies. The major differential diagnosis was cervical carcinoma which can present with very similar macroscopic lesions and symptoms, although histology discriminate between the two. Another frequently considered diagnosis, that led to an inapropriate treatment in one case (2), is genital tuberculosis although it is far rarer than the former but causes granulomas as in granulomatosis with polyangiitis. This particular differential diagnosis can be difficult since vasculitis can be absent due to small sampling size, as the results of our second set of biopsies demonstrated.

Of note, the delay between metrorrhagia and the definite diagnosis of genital involvement was of nineteen months in our case, the patient being heavily inconvenienced during that time. Of those cases in which chronology is available, the average time between the initial presentation and the diagnosis is of 21 months. We hope this report will serve to avoid such long diagnostic delays.

In eight out of ten reported cases, involvement of the uterine cervix presented during a relapse of the disease and in seven out of these ten cases, cervical disease was, at least initially, isolated from any other disease manifestation. There does not seem to be any particular correlation to another organ's involvement, either concurrently or prior to the cervical involvement.

In one of the cases (2), the patient received rituximab therapy, but the indication was not her gynaecological involvement, which had been resolved through cyclophosphamide and prednisone therapy at the time, but an upper airway disease which had proven refractory to standard of care and endoscopic intervention.

In conclusion, we report a new case of an unusual presentation of granulomatosis with polyangiitis, namely the uterine cervix and the upper vagina. In Table. Cases of gynecological involvement in granulomatosis with polyangiitis.

Ref	Age	Presentation	Initial presentation	Diagnosis delay	ANCA status	Treatment	Outcome	Diagnostic method
#1	45	Isolated relapse	Unspecified	Undisclosed	c-ANCA 1/160	Cyclophosphamide and prednisone	Resolved in 3 months	Pap smear and biopsy
#2	82	Isolated relapse	Cervix then lung	4 years	c-ANCA 1/320	Cyclophosphamide and prednisone	Favorable	Lung and cervix relapse
#3	32	Relapse with kidney and lung disease	Nose and pulmonary	1 year	c-ANCA 1/640	Cyclophosphamide and prednisone	Lost to follow-up	Biopsy
#4	80	Isolated relapse	Dialysis	16 months	c-ANCA 1/80	Not available	Died day after biopsy	Hysteroscopic biopsy
#5	64	Relapse with tracheal involvement	Unspecified	3 weeks	anti-PR3 14 IU/ml	Cyclophosphamide and prednisone	Resolution	Cervix biopsy, lung disease
#6	42	Isolated relapse	ENT and cervix	5 years	anti-PR3 >100 IU/ml	Cyclophosphamide and prednisone	Two year remission	ENT involvement
#7	71	Isolated primary	Not available	1 year	PR3+	Surgery and azathioprine	Surgery ineffective, good result with azathioprine	ENT disease
#8	61	Isolated relapse	ENT	Undisclosed	Not availbale	Prednisone	Died five years later, unknown cause	Biopsy re-read after radiotherapy
#9	55	Relapse with URT involvement	Nose and URT	First work-up	c-ANCA 1/160	Cyclophosphamide and prednisone	Resolved in one month	Biopsy and ENT symptoms
Our case	34	Isolated relapse	Skin, joints, sinus	19 months	anti-PR3 101 IU/ml	Rituximab	Near resolution in six months	Conization

particular, we show – for the first time – a good response to rituximab therapy, proven through the favourable evolution of direct colposcopy examination and confirmed by repeated FDG-PET scan.

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