Ano-genital granulomatosis and Crohn's disease: a case series of males presenting with genital lymphoedema

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Short title: Ano-genital granulomatosis and Crohn’s disease in male patients
Abstract

Background and Aims

Ano-genital granulomatosis is a rare chronic granulomatous condition of the skin that causes lymphoedema of the external genitalia. There is a reported association with Crohn's disease. Mechanisms of disease, and optimal methods of treatment are poorly understood.

Methods

A retrospective case note review of 25 male patients with ano-genital granulomatosis presenting with genital lymphoedema was performed to determine the clinical and histopathological features of this condition and its relationship to intestinal Crohn's disease.

Results

A combination of penile and scrotal oedema was reported at presentation in 80% of patients. 40% of patients had associated intestinal Crohn's disease. The average time from symptom onset to diagnosis was 52.7 months. Half of cutaneous biopsies contained non-caseating granulomas and 14% contained intra-lymphatic granulomas. 72% of patients responded to oral steroids initially but recurrence was common. Complete or partial response was achieved in 60% of patients treated with azathioprine. Three of 6 patients responded to anti-TNF therapy. A small proportion of patients required circumcision or de-bulking surgery for more debilitating disease.

Conclusions

Ano-genital granulomatosis is a rare condition that presents with genital lymphoedema and there is frequently a protracted delay in diagnosis. There is a very strong association with intestinal Crohn's disease. Genital lymphoedema associated with gastrointestinal symptoms should prompt careful evaluation to exclude both ano-genital granulomatosis and Crohn's disease.
key words

Ano-genital granulomatosis

Crohn’s disease

Lymphoedema
Introduction

Ano-genital granulomatosis (AGG) is a rare idiopathic chronic inflammatory condition that presents with progressive and persistent genital and peri-genital oedema, and usually non-caseating granuloma are revealed on skin biopsy. Although the condition was first formally described in the 1970s, the medical literature has largely been limited to case reports and small case series. Reports have indicated a possible overlap with Crohn’s disease (CD).

The condition usually manifests as chronic penile, scrotal, vulval or perianal oedema but may affect the more extensive peri-genital area including the mons pubis, buttocks and natal cleft. Episodes of secondary cellulitis occur frequently as with many other forms of lymphoedema. Histology from affected skin typically demonstrates the presence of non-caseating granulomas and a chronic inflammatory infiltrate, although granulomas may be sparse and easily missed. The exact underlying aetiology is not clearly understood, but a variety of both infective and inflammatory conditions have previously been associated with this condition including sarcoid, Behcet’s, Wegener’s granulomatosis, tuberculosis and syphilis.

Where AGG and CD co-exist genital lymphoedema may result from the direct extension of ano-rectal CD into the affected skin, but equally can occur without contiguity between skin and gastrointestinal tract. Impaired lymphatic drainage has previously been implicated in the pathogenesis of CD. Similar histopathological changes that occur in AGG have been described in intestinal Crohn’s disease, which may explain the observed overlap seen between these conditions.

Little is known about the optimal management of AGG, but the use of antibiotics, corticosteroids, and Tumour Necrosis Factor inhibitors (aTNF) in the management of AGG have all been described in case reports. A recent case series has reported the clinical features of vulval lymphoedema in 22 females with and without CD. We therefore aimed to characterise the clinical features,
histological findings, response to treatment and overlap with CD in a cohort of 25 male patients with a confirmed diagnosis of AGG presenting with genital swelling to a national lymphoedema unit.
Methods

This was a retrospective descriptive case series. Patients with genital lymphoedema and a suspected diagnosis of AGG were referred to our centre where they were reviewed in the joint gastroenterology and lymphoedema clinic. Initial evaluation included a full clinical history, a detailed physical examination, and assessment of the pattern of genital (and peri-genital) lymphoedema. After acquiring full patient consent, digital photographic images were made of the extent of genital oedema, as a reference to assess treatment response. Samples for histological diagnosis were taken at the first clinic assessment, usually with a punch biopsy under local anaesthetic. Histology was reported by two specialist histopathologists. All potential cases of the condition were discussed by the Gastroenterology-Lymphoedema team at a multi-disciplinary team meeting and agreed cases of AGG were collated in a database.

Clinical-pathological data was collected retrospectively (CA and RM) for this study. The clinical notes, letters, electronic records and histology were retrospectively reviewed for each confirmed case of AGG. Co-existent medical conditions were ascertained from historical clinical records and/or confirmation with the patient. Details of medical and surgical treatments were obtained by case note review.
Results

Demographics

We identified 25 male patients with a confirmed diagnosis of AGG from the database between August 2006 and October 2015 (Table 1). Mean follow-up was 24.4 months (range 1-81 months). Twenty-four patients were Caucasian (one Asian). Mean age at diagnosis was 32.2 years (range 7-66 years). The mean number of months between self-reported symptom onset and formal diagnosis was 52.7 months (range 6-264 months). The hospital specialties that the patients were initially referred to were: Dermatology (56%), Urology (32%) and others (12% - including genitourinary medicine, paediatrics and plastic surgery).

Clinical Presentation

The commonest anatomical site for oedema was the penis (92% of patients), and scrotum (80%). Figure 1 demonstrates the characteristic lymphoedematous appearance of the external male genitalia in two patients suffering from AGG, one of whom also had intestinal CD. The combination of penile and scrotal involvement was seen in 80% of patients. Table 2 shows the respective areas of anatomical involvement in AGG patients with and without CD. Ulceration and fissuring was not a common presenting feature in these patients.

All patients described a chronic progressive disease pattern characterised by relapsing and remitting periods of increased genital lymphoedema, interspersed with periods of erythema, resulting from secondary cellulitis. Patients also frequently described problems with urinary flow and difficulties with sexual intercourse.

Co-morbidities
13 patients (52%) had other medical diagnoses at the time of AGG diagnosis. Additional co-morbidities are reported on Table 1 (and additional table 1 in appendix), although notably, these included ulcerative colitis (n=1), psoriasis (n=3) and orofacial granulomatosis (n=4).

**Gastrointestinal symptoms and associated Crohn’s disease**

44% of patients reported concurrent gastroenterological symptoms at presentation. Symptoms described included diarrhoea (73%) and abdominal pain or discomfort (36%). In total, following investigation, 10 patients (40%) were found to have clinical, endoscopic and radiological findings consistent with Crohn’s disease (CD). Five CD patients (50%) had the disease diagnosed prior to their AGG diagnosis. Seven patients with Crohn’s had available colonoscopy reports: normal (n=1), colonic disease (n=3), terminal ileal disease (n=2), and terminal ileal plus rectal penetrating disease (n=1).

**Histology**

Full histology was available for 22 patients (88%). Two patients had biopsy and histology assessed at the referring hospital and found to be consistent with AGG. One patient refused genital biopsy, but it was agreed that his clinical presentation was consistent with a diagnosis of AGG. Table 3 categorises the frequency of the histological findings associated with AGG. All samples contained a lymphocytic predominant chronic inflammatory infiltrate. 57% of the biopsies contained identifiable non-caseating granulomas, and 14% contained intra-lymphatic granulomas. Figure 2 demonstrates some of the pertinent histological findings associated with AGG.

**Management and treatment response**

The medical treatments and the proportion of patients reporting response in AGG symptoms is summarised in Figure 3.

**Supportive therapy** - all patients were referred to lymphoedema clinical nurse specialists and received compression garments and instructions on penile bandaging in cases of severe penile
lymphoedema, although standard lymphoedema treatment had limited efficacy without addressing the underlying inflammatory component of the disease process.

**Oral antibiotics** - antibacterial agents were used in 84% of patients. They were predominantly prescribed as long term prophylaxis (1-6 months) to prevent episodes of secondary cellulitis. 76% of patients reported an improvement in their AGG symptoms with antibiotic use. Prophylactic antibiotics used included; doxycycline 100mg OD, co-trimoxazole 960mg OD, co-trimoxazole 480mg BD, co-amoxiclav 375mg TDS, clindamycin 250mg OD and trimethoprim 200mg OD.

**Oral corticosteroids** - oral steroid therapy, were used in 72% of the patients (usually in combination with antibiotics), with 72% of patients treated showing initial improvement in lymphoedema, although relapse on tapering the doses was common. Prescription data was available for 11 patients receiving 12 reducing courses of prednisolone. Mean starting prednisolone dose was 34.1mg (range 20-50mg). Dose reduction intervals were generally between 7-14 days per drop in dosage.

**Immunomodulators** - Azathioprine (AZA) was used in 60% of the patients. In total, 60% made a complete or partial response to treatment, as demonstrated by an improvement in swelling. Complete prescribing data was available for 11 patients. Mean dose of AZA was 131.4mg/day (range 50-200mg/day) with a mean duration of treatment 18.7 months (range 5-46 months). 7 of the 10 AGG patients with Crohn's were treated with AZA. From the 15 non-CD AGG patients, 8 were treated with azathioprine, of which 87% reported improvement on symptoms. Mycophenolate mofetil (MM) was used in one non-CD AGG patient (1g BD, 42 months) whose AGG symptoms improved with this medication. One AGG patient with CD had to stop MM due to side effects.

**Tumour Necrosis Factor Inhibitors (aTNF)** - aTNF therapy was used in 6 AGG patients, all of whom had a co-diagnosis of CD. Standard induction regimes were used for both infliximab and adalimumab. Four patients were treated with infliximab, and 2 with adalimumab. A total of 3 patients gained benefit with reduction in genital lymphoedema.
Surgical therapies

Although surgery is not considered curative for AGG, it can be employed to reduce the volume of lymphoedema resulting from the underlying inflammatory changes. Indications for surgery included; failure of medical treatment, difficulties with micturation, difficulties with sexual intercourse, and cosmetic reasons. Two main surgical techniques were used; circumcision (n=6) of which 83% reported improvement in symptomology; or de-bulking surgery (n=4), with all patients reporting initial improvement. The preferred surgical de-bulking procedure involves excision of lymphoedema tissue followed by split skin grafting and/or excision of excess scrotal tissue with primary closure. The mean time to surgery from AGG diagnosis was 13 months. No immediate post surgical complications were reported in the 4 patients who underwent de-bulking. By approximately one to two years post de-bulking surgery, all four patients had minimal recurrence of penile oedema. One patient had redeveloped severe penile oedema by four years post surgery, and was being considered for a further de-bulking procedure.
Discussion

Key findings

To our knowledge, this is the largest study of male patients with AGG, 40% of whom were found to have intestinal CD. The majority of patients initially presented with chronic penile and scrotal oedema. There was often a protracted delay between first reported symptoms and formal diagnosis, approaching a mean of 5 years. Skin biopsy from affected areas revealed non-caseating granulomas in more than half of patients, and 14% had intra-lymphatic granulomas. All 25 patients reported a chronic progressive disease pattern characterised by recurring episodes of genital oedema with or without a secondary cellulitis. Almost three quarters of patients experienced short-term improvement with oral corticosteroid therapy, but most needed second line treatment in the form of immunomodulators, or aTNF therapy to achieve a sustained response.

Findings in relationship to other studies

40% of our cohort had both AGG and CD in keeping with the findings of previous case reports. In a review of previously reported cases of AGG, 36% of patients had concomitant CD.\textsuperscript{1} It is important to recognise that AGG may precede the diagnosis of CD by many years,\textsuperscript{17} but equally can manifest following confirmation of CD. In our series, half of patients were diagnosed with CD following their AGG diagnosis, and in this respect resembles oro-facial granulomatosis (OFG).\textsuperscript{18}

The considerable period between self-reported first symptoms and formal diagnosis seen in our cohort is similar to that reported in a case series of female patients with vulval Crohn’s.\textsuperscript{16} This presumably relates to clinicians unfamiliarity with the condition, resulting in misdiagnosis and inappropriate specialist referral. Patient embarrassment may also be a contributing factor to delayed presentation.\textsuperscript{19}
Our study is confined to male patients with confirmed AGG, but we do not feel this is a distinct clinical entity exclusive to males as we have also managed female patients with this condition presenting with vulval oedema very much as described previously by Laftah et al which this research group have defined as “vulval Crohn’s disease”. Furthermore, in a summary of historical individual case reports and series, about 40% of patients with AGG were male.

The presence of non-caseating granulomas is a common finding in patients with AGG and was seen in more than half of our cohort. The occurrence of intra-lymphatic granulomas may represent a potential mechanism through which lymphatic drainage is impeded leading to the genital lymphoedema and subsequent inflammation. We found evidence to support this disease mechanism, with 14% and 52% of our biopsies showing intra-lymphatic granulomas and lymphatic dilatation respectively. Intra-lymphatic granulomas and lymphangiectasia have also been described in OFG. OFG is a rare clinical entity manifest by lymphoedema of the face and oral cavity and shares many of the histological characteristics of AGG. OFG is also reported to overlap with intestinal CD in 20-40% of cases. Notably in our series, four patients had OFG, 2 of whom had a triad of AGG, OFG and CD.

Impairment of lymphatic drainage in intestinal CD has also been linked to granulomatous obstruction of lymphatic flow, lymphangiectasia and lymphangitis. In one study, 46% of granuloma found within biopsies taken from patients with intestinal CD were related to or in close proximity to lymphatic vessels. These observations possibly point to a common pathway between the two clinical entities. Certainly, a role for lymphatic insufficiency in the aetio-pathogenesis of CD has previously been proposed.

The nomenclature is confusing and it has been argued by some authors that AGG is indistinguishable from cutaneous metastatic CD. However, we propose that AGG and MCD are two separate presentations of cutaneous granulomatous inflammation as a result of CD. Metastatic Crohn’s disease (MCD) is a rare cutaneous granulomatous disorder where patients present with pruritic
erythematous plaques or nodules that are non-contiguous with the gastrointestinal tract, and separated from it by normal skin. MCD may affect the face, trunk and limbs, but may also affect genital skin. Histological analysis of these lesions confirms the presence of a non-caseating granulomatous inflammatory infiltrate.

AGG may appear similar to MCD to some readers because of the reported presence of granuloma within the skin. We hypothesise that AGG is in fact a separate entity based on three factors. Firstly, the defining feature of AGG is the presence of swelling and lymphoedema, which is not a feature of MCD. Secondly, AGG only affects the ano-genital region, whereas MCD frequently affects non-genital skin. Finally, over 98% of patients with MCD have, or will subsequently develop a co-diagnosis of CD, whereas co-diagnosis in AGG is only approximately 40%.

Studies addressing optimal management of AGG are lacking. The use of antibiotics has been previously described in the management of AGG with mixed success. In this case series, antibiotics were used frequently where secondary cellulitis was suspected, and as prophylaxis against further episodes. Infection, particularly cellulitis, is common in patients with AGG probably as a direct result of impaired immune surveillance within regions of damaged lymphatic drainage. Antibiotics are likely to be of benefit in acute flares where a secondary cellulitis may complicate the underlying granulomatous inflammation. Low dose antibiotic prophylaxis may also be indicated, although their role in preventing disease progression is unknown, and it is plausible that recurrent cellulitis may cause irreversible lymphatic damage.

Oral corticosteroid therapy provided short-term benefit in our patients, often with initial improvement in oedema. Steroid treatment is usually ineffective in primary lymphoedema as the impaired lymphatic drainage occurs as a result of a genetically predetermined weakness within the lymphatic channels. However, their action on the inflammatory component of AGG may explain their efficacy in this condition. The efficacy of corticosteroids in the long-term is limited since we have observed oedema frequently recurs on cessation of treatment.
Immuno-modulators such as azathioprine (AZA) may have a role in the long-term treatment of AGG. They have established efficacy in the treatment of intestinal CD and are also used frequently in management of OFG.\(^{23}\) In our series, clinical improvement was found in both patients with and without associated CD. Two thirds of our cohort treated with AZA had symptomatic improvement. Laftah et al reported similar response rates in a cohort of female patients with vulval CD.\(^{16}\)

Our experience with aTNF therapy was limited to 6 patients, all of whom had CD, and half of which reported symptomatic improvement in AGG symptoms. Previous case reports have indicated response in both patients with AGG, with and without intestinal CD.\(^{5,16}\)

**Conclusion**

Ano-genital granulomatosis is a rare condition and usually presents with penile and scrotal lymphoedema in males. Unless the clinician is vigilant, there may be a protracted delay in diagnosis. In this largest case series, we have confirmed a strong association with Crohn's disease. Genital lymphoedema in association with gastrointestinal symptoms should prompt careful evaluation to exclude AGG and intestinal Crohn's disease. A variety of treatment options for AGG exist and many of the agents used in the management of Crohn's also appear effective in AGG. However, further studies are required to define optimal treatment in this condition.
Funding

The project did not receive any funding.

Acknowledgements

CA extracted and analysed all the data, and wrote the manuscript. KG assisted with case identification, data collection and interpretation, and drafting of the final manuscript. RM assisted with case identification, extraction and analysis of data, and the drafting of the final manuscript. HC assisted with case identification, histological sample retrieval and descriptions, and the drafting of the final manuscript. PM assisted with the development of the concept of the paper, case identification, data analysis and interpretation, and drafting of the final manuscript. RP assisted with the development of the concept of the paper, case identification, data interpretation and drafting of the final manuscript.

Conflicts of Interest

None.
References


Legends

Table 1 legend

*a co-morbidities included: orofacial granulomatosis (n=4), psoriasis (n=3), ischaemic heart disease, hypertension, type 2 diabetes, ulcerative colitis, hydradenitis suppurativa, connective tissue disease, Coeliac’s disease, Hirschsprung’s disease, hypospadias, primary sclerosing cholangitis (n=1). aTNF - anti-tumour necrosis factor. Full details submitted as an appendix table.

Table 2 legend

No significant differences observed between groups. CD - Crohn’s disease, AGG - ano-genital granulomatosis

Figure 1 legend

A - typical appearance of penile oedema in a male patient presenting with AGG. The oedema affects the foreskin and shaft tissue and can cause difficulties with micturation and erection. In this patient, no features of intestinal CD were found on small bowel MRI, endoscopy or colonoscopy. B - AGG in an adolescent presenting with penile oedema before the onset of small and large bowel CD. Note the erythematous penile shaft swelling, and the subtle lymphoedema of the scrotum

Figure 2 legend

A - skin biopsy showing a well formed non-necrotising granuloma in the dermis associated with a mild lymphocytic infiltrate. The granuloma is immediately adjacent to a vascular channel. B - a non-necrotising granuloma directly adjacent to a lymphatic vessel. An aggregate of histiocytes and lymphocytes is present within the dilated lumen of the vessel.
(intralymphatic histiocytosis). **C** - a loosely formed non-necrotising granuloma next to a lymphatic channel. **D** - an aggregate of histiocytes within the dilated lumen of a lymphatic channel.

**Figure 3 legend**

**Figure 3**: histogram showing numbers of patients exposed to various treatments, and proportion of patients that did/didn’t experience improvement. Numbers shown in columns. Abx - antibiotics, po C/S - oral corticosteroid, Aza - azathioprine, Myc - mycophenolate, aTNF - anti tumour necrosis factor inhibitors, Sx - symptoms
Tables
Table 1: Summary of demographics, clinical features and treatments received by 25 male patients with AGG

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>AGG patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 25</td>
</tr>
<tr>
<td>Mean age at diagnosis</td>
<td>32.2 years</td>
</tr>
<tr>
<td></td>
<td>(range 7-66)</td>
</tr>
<tr>
<td>Mean time from symptom onset to</td>
<td>52.7 months</td>
</tr>
<tr>
<td>diagnosis</td>
<td>(range 6-264)</td>
</tr>
<tr>
<td>Other co-morbidities *</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Co-diagnosis of Crohn’s disease</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Treatments received</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>aTNF inhibitors</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Requirement for circumcision</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Requirement for de-bulking surgery</td>
<td>4 (16%)</td>
</tr>
</tbody>
</table>

* co-morbidities included: orofacial granulomatosis (n=4), psoriasis (n=3), ischaemic heart disease, hypertension, type 2 diabetes, ulcerative colitis, hydradenitis suppurativa, connective tissue disease, Coeliac's disease, Hirschsprung's disease, hypospadias, primary sclerosing cholangitis (n=1). aTNF - anti-tumour necrosis factor. Full details submitted as an appendix table.
Table 2: proportion and distribution of anatomy affected in male patients diagnosed with AGG both with and without Crohn's disease

<table>
<thead>
<tr>
<th>Anatomy affected by lymphoedema</th>
<th>AGG no CD n = 15</th>
<th>AGG + CD n = 10</th>
<th>All AGG n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penis</td>
<td>87%</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Scrotum</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Mons pubis</td>
<td>27%</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>Buttock</td>
<td>27%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Perineum</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Peri-anal</td>
<td>13%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Natal cleft</td>
<td>13%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

No significant differences observed between groups. CD - Crohn's disease, AGG - ano-genital granulomatosis
Table 3: Histological features from genital skin biopsies in male patients with ano-genital granulomatosis

<table>
<thead>
<tr>
<th>Histological parameter</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomas</td>
<td>57</td>
</tr>
<tr>
<td>Multi-nucleate giant cells</td>
<td>24</td>
</tr>
<tr>
<td>Chronic inflammatory infiltrate</td>
<td>100</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>100</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>19</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>14</td>
</tr>
<tr>
<td>Plasma Cells</td>
<td>57</td>
</tr>
<tr>
<td>Histiocytes</td>
<td>43</td>
</tr>
<tr>
<td>Mast cells</td>
<td>10</td>
</tr>
<tr>
<td>Epidermal changes</td>
<td>67</td>
</tr>
<tr>
<td>Oedema</td>
<td>52</td>
</tr>
<tr>
<td>Dilated lymphatic vessels</td>
<td>52</td>
</tr>
<tr>
<td>Intra-lymphatic granulomas</td>
<td>14</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>14</td>
</tr>
</tbody>
</table>
Figures

Figure 1: classic presenting features of males with AGG

A - typical appearance of penile oedema in a male patient presenting with AGG. The oedema affects the foreskin and shaft tissue and can cause difficulties with micturation and erection. In this patient, no features of intestinal CD were found on small bowel MRI, endoscopy or colonoscopy. B - AGG in an adolescent presenting with penile oedema before the onset of small and large bowel CD. Note the erythematous penile shaft swelling, and the subtle lymphoedema of the scrotum.
**Figure 2**: Histological findings from skin biopsies of male patients with AGG

A - skin biopsy showing a well formed non-necrotising granuloma in the dermis associated with a mild lymphocytic infiltrate. The granuloma is immediately adjacent to a vascular channel.  

B - a non-necrotising granuloma directly adjacent to a lymphatic vessel. An aggregate of histiocytes and lymphocytes is present within the dilated lumen of the vessel (intralymphatic histiocytosis).  

C - a loosely formed non-necrotising granuloma next to a lymphatic channel.  

D - an aggregate of histiocytes within the dilated lumen of a lymphatic channel.
**Figure 3**: histogram of medications prescribed and associated self-reported improvement in lymphoedema symptoms in 25 males with AGG

Whole numbers shown in columns. Abx - antibiotics, po C/S - oral corticosteroid, Aza - azathioprine, Myc - mycophenolate, aTNF - anti tumour necrosis factor inhibitors, Sx - symptoms