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Experience from the first UK inter-regional specialist multi-disciplinary meeting in the diagnosis and management of IgG4-Related Disease

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Abstract

IgG4-related disease (IgG4-RD) is a complex multi-system fibro-inflammatory disorder, requiring diagnostic differentiation from malignancy and other immune-mediated conditions, and careful management to minimise glucocorticoid-induced toxicity and prevent progressive organ dysfunction. We describe the experience of the first inter-regional specialist IgG4-RD multi-disciplinary meeting (MDM) incorporating a broad range of generalists and specialists, held six-weekly via web-link between Oxford University Hospitals and University College London Hospitals. Over three-years, there were 206 discussions on 156 patients. Of these, 97 (62%) were considered to have definite or possible IgG4-RD; 67% had multi-organ involvement and 23% had a normal serum IgG4. The average number of specialist opinions sought prior to MDM was four per patient. Management was changed in the majority of patients (74%) with the treatment escalation recommended in 61 cases, including 19 for rituximab. Challenges arose from delays and mis-diagnosis, cross-speciality presentation, and the management of sub-clinical disease. Our cross-discipline IgG4-RD MDM enabled important diagnostic and management decisions in this complex multi-system disorder, and, can be used as a model for other centres in the UK.

Keywords

IgG4-related disease, multi-disciplinary, rituximab, inflammation

Introduction

IgG4-related disease (IgG4-RD) is a recently defined multisystem fibro-inflammatory condition that has been described in almost every organ.[1] It is classified as a 'rare disease', although there is sparse epidemiological data outside of Asia and none that fully incorporates its multi-system nature.[2]

A diagnosis of IgG4-RD presents multiple challenges to the clinician. First, the typical presentation with mass-forming lesions and/or strictures and the presence of local and/or generalised lymphadenopathy makes it difficult to differentiate from malignancy, whilst organ-specific features often mimic other immune-mediated chronic inflammatory conditions.[3–5] This can lead to unnecessary surgical resection for presumed cancer (34% underwent surgical resection for presumed pancreatobiliary malignancy in one series),[6] inappropriate delay in treatment (delayed corticosteroids in patients misdiagnosed with primary sclerosing cholangitis)[7] and misinformation regarding disease course and prognosis to patients and their relatives. Second, clinical presentation varies with the organ system involved, so patients will present to a number of general and specialist physicians and/or surgeons who may find it difficult to unify a diagnosis, leading to delays in diagnosis and possible disease progression. Third, no single investigation can confirm the diagnosis, which relies on a combination of clinical signs, lab-based biochemistry and immunology, radiology and histopathological findings.[8–10] Indeed, serum IgG4 can be normal in 20-40% of IgG4-RD patients with insufficient sensitivity and specificity for stand-alone use.[11,12] Diagnostic guidelines often favour one organ system and rely on adequate histology sampling and high-quality assessment to confirm a diagnosis, which is difficult to obtain.[8,10,13] New classification criteria developed by the International IgG4-RD Classification Criteria Committee[14] with a focus on diagnostic exclusion and less emphasis on histology may be more robust in many cases where tissue is unavailable or interpretation is equivocal.

Although a proportion of IgG4-RD patients will undergo spontaneous disease regression, the majority of these will later relapse[15] and untreated active disease results in progression to fibrosis and end-organ dysfunction.[16] There is international consensus that all symptomatic patients and some asymptomatic patients with IgG4-RD require treatment to induce disease remission.[17] Observational and randomised studies[18] have shown IgG4-RD to be highly corticosteroid responsive. However, relapse is common, occurring in 20-60% of patients.[19,20] Furthermore,

glucocorticoid-toxicity is frequent in IgG4-RD, with a recent study reporting 31/43 steroid treated patients experiencing steroid-related adverse events.[21] Although immunomodulatory drugs including azathioprine, methotrexate, tacrolimus and mycophenolate mofetil are often used as steroid-sparing agents, there remains a paucity of documented evidence regarding their efficacy.[17] Rituximab, a B-cell depletion agent, has shown promise in those intolerant of steroids and with refractory IgG4-RD.[22,23] NHS England has recently commissioned its use as third-line for IgG4-RD in the UK, with implementation of strict criteria including its prescription through a specialist IgG4-RD MDM and recommendation of a national registry of IgG4-RD patients. Novel therapies under evaluation include Iguratimod, Abatacept and Reukimid with Rituximab, all currently registered for clinical trials in IgG4-RD with the US National Institutes of Health.

Our group initially founded the UK IgG4-RD Study in 2010 and established the first European IgG4-RD registry database in 2014. To address the challenges presented by this disease, we established a supra-regional specialist IgG4-RD multi-disciplinary team meeting (MDM) incorporating generalists and a broad range of specialists to advise on the diagnosis and management of these complicated cases. Pooling resources, clinical experience and insight into one functional team through collective discussion and individualisation of treatment, MDM's are crucial in the diagnosis and management of both malignant and benign diseases.[24] This is increasingly important with the growing armamentarium of immunomodulatory and biological agents at our disposal. We present our collective experience from the first year of our supra-regional specialist IgG4-RD MDM, and, describe how collaborative working in the field of IgG4-RD can lead to improved care for patients with more accurate and timely diagnoses as well as streamlined management pathways.

Methods

Set up of the IgG4-RD MDM

Oxford University Hospitals (OUH) and University College London (UCL) have built up extensive experience in the diagnosis and management of IgG4-RD patients, first describing patients with predominantly IgG4-related autoimmune pancreatitis (AIP) and sclerosing cholangitis (IgG4-SC) in 2007.[25] Over the subsequent years, specialists in these centres have received referrals from local, regional and national centres to guide decision making in these complex patients. Review of diagnosis and management was previously performed on an ad-hoc basis through the regional

Gastroenterology and Hepatopancreatobiliary medicine MDMs in each hospitals, with informal discussion with rheumatology colleagues for those with extra-pancreatobiliary disease.[24] A dedicated joint Oxford-UCL multi-speciality IgG4-RD MDM was established in November 2016 in response to an increase in patient referrals with possible IgG4-RD, increasing complexity of cases with multi-organ involvement, controversies on optimal treatment strategies, and close clinical and research collaboration between the two centres.

Objectives of the IgG4-MDM

The broad goals of the joint IgG4-MDM included (1) Establishing a diagnosis of definite or possible IgG4-RD. This required review of clinical, immunological, radiological and histopathological evidence to support a diagnosis. In those where a diagnosis of IgG4-RD was not supported, advice was given for further investigations required to achieve this and/or an alternative diagnosis was sought where possible, with referrals made to the appropriate speciality to continue follow-up. (2) Agreeing a management plan. This may include a conservative watch-and-wait approach, requesting further laboratory measurements (e.g. serum IgG4 titres), radiological imaging (e.g. CT-PET) and/or histological assessment (E.g. EUS and core pancreatic biopsy), initiating first or second line treatment, discontinuation of treatment, and approval of restricted third line treatment (e.g. Rituximab). (3) Assessment of treatment response and disease course, with an emphasis on laboratory parameters and radiological response. (4) Recruitment of patients into clinical and translational research studies.

Structure of the IgG4-RD MDM

Referrals are made on a dedicated proforma, sent to an MDM email address at each site, and details collected for audit purposes. A 75-minute teleconference meeting takes place once every six weeks via a video-link connecting the teams in Oxford and London. External sites can also dial-in via phone or video-link. The MDM is chaired by Consultant Physicians at each site (GW at UCL and EB/EC at OUH). Core members include consultant radiologists, histopathologists, gastroenterologists/hepatologists, rheumatologists, and general physicians with an interest in IgG4-RD. Visiting specialists include clinical immunologists, neurologists, haematologists, respiratory physicians, nephrologists, ophthalmologists, ENT and oral medicine physicians and surgeons. Research fellows, clinical registrars, junior doctors and students are all encouraged to attend.

Outcome data from the IgG4-MDM

MDM outcomes are agreed by consensus and recorded on a formalised proforma at each site, and on a web linked Rheumatology Assessment Database Innovation in Oxford (RhADIO), integrated with the electronic patient record at OUH. All patients with IgG4-RD are invited to be included in a prospective IgG4-RD national registry database held at OUH.

Diagnostic criteria for IgG4-RD

A diagnosis of IgG4-RD was made in accordance with the Mayo HISORt criteria for patients with AIP and IgG4-SC[8] and the International Consensus Diagnostic Criteria (ICDC) for AIP.[26] Patients with type II AIP were excluded.[27] Patients with systemic disease were diagnosed using the Japanese Comprehensive Diagnostic Criteria (JCDC) for systemic IgG4-RD.[9] The Boston Consensus Histopathological Criteria for IgG4-RD were applied to all patients with biopsy and resection specimens available.[10]

Laboratory measurements

Routine haematology and biochemistry including liver function, renal function and inflammatory markers were assessed. Total serum IgG and IgG4 were measured by nephelometry. Elevated serum IgG and IgG4 were defined by institution range. Complement proteins (C3 and C4 levels) were requested to support diagnosis. Tissue-specific autoantibodies were requested to suggest alternative diagnoses, such as antineutrophil cytoplasmic antibodies (ANCA), double stranded-DNA, anti-SSA (Ro) and anti-SSB (La) antibodies, and Cryoglobulins.

Radiological assessment

In order to assess appreciate multi-organ involvement and assess subclinical disease, radiological imaging reviewed included CT chest, abdomen and pelvis, Magnetic Resonance Cholangiopancreatography (MRCP), Endoscopic Retrograde Cholangiopancreatography (ERCP), Magnetic Resonance Imaging (MRI) of the head and neck and Computed Tomography-Positron Emission Tomography (CT-PET).

Histological assessment and tissue immunostaining

All biopsy and resection specimens were assessed for classical morphological features of IgG4-RD, specifically a lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis (with variable presence of eosinophils) in accordance with consensus histological criteria.[10] Tissues were immunostained with IgG and IgG4 monoclonal antibody. The IgG4 count was reported as the average number of IgG4-positive plasma cells in 3 high-powered fields (HPF). An elevated IgG4 count in a

biopsy specimen was defined in accordance with consensus criteria for each organ. In those with an elevated IgG4 count, an IgG4 to total IgG ratio was calculated; an elevated IgG4:IgG ratio was defined as >40%.

Results

Referral patterns: speciality and geographical location

During the three years 2016-2019 there were twenty-one MDMs, with a total of 156 patients referred for a total of 206 MDM discussions. Over time there has been a steady increase in the average number of referrals to the IgG4 MDM. Whilst the number of case discussions relating to patients referred from the MDM host institutions remained relatively constant, regional and national cases have shown a year on year increase (**Figure 1**). Referrals were received from multiple institutions throughout the UK and Ireland (**Figure 2A 2**), with the majority from the South East and Greater London regions. Referrals came from a diverse range of medical and surgical specialities, including paediatrics (**Figure 3**). Almost a third of patients (49/156) were referred from pancreatobiliary medicine and hepatology, and one thirteenth of patients (12/156) from rheumatology.

Patient referrals: demographics and clinical characteristics

Of the 156 patients referred to the IgG4 MDM, the median age was 60-years (range 11-90 years), and the male to female ratio was 3.6:1. At the time of referral, serum IgG4 levels were recorded in 136 patients. The majority had an elevated serum IgG4 (sIgG4) titre (>1 ULN) (97/136; 71%) recorded by the referring physician. Ninety-eight percent (153/156) patients had cross-sectional imaging and most had had a previous biopsy and/or resection specimen for review (107/156, 69%), with IgG4 immunostaining performed in most and IgG4:IgG ratio recorded in only a minority.

Referral pathway

Patients had been seen by an average of four specialists at the time of referral to the MDM (range 1-6). 131/156 (84%) were new referrals to the MDM for diagnostic clarification and advice on subsequent management, and 25 were re-discussions (diagnosis confirmed by historic MDM at OUH or UCLH) and specifically referred for management advice.

Clinical Diagnosis

Of the 156 patients discussed, 97 patients (62%) were given a diagnosis of possible or definite IgG4-RD. 60 met one or more of the diagnostic criteria for IgG4-RD, 37 did not meet diagnostic criteria per se, but were considered by consensus by the MDM members to have ‘possible IgG4-RD’ based on supportive features. The remaining 59 patients (38%) did not meet diagnostic criteria and were considered not to have IgG4-RD, with alternative diagnoses sought.

Definite IgG4-RD: 60 patients met diagnostic criteria and were diagnosed with IgG4-RD. Of these, 46 (77%) had an elevated serum IgG4 level. 45 (75%) had multiple organ disease (\geq two organs) confirmed by a combination of clinical signs, laboratory results and radiology. Forty-two patients had a histological sample (resection and/or biopsy) available for review, which was felt to be sufficient to support a diagnosis in 39 cases. Of those with histological samples, 30/42 had \geq two morphological criteria, IgG4 immunostaining and an IgG4:IgG ratio calculated to meet the Boston Histopathological criteria.

Possible IgG4-RD: 37 patients did not meet diagnostic criteria but had supportive features and were diagnosed with possible IgG4-RD. Of these, 22 (59%) had an elevated serum IgG4 level and 20 (54%) had multiple organ disease. Fifteen had a histological sample (resection and/or biopsy) that was felt to be sufficient to support a diagnosis. The differential diagnoses suggested for those with possible IgG4-RD are listed in **Table S2**. We recommended long-term clinical follow-up in all those within this category.

Organ involvement in IgG4-RD may be sub-classified into four broad phenotypic groups.[28] Overall, there was good representation from all four groups in those with definite and possible IgG4-RD (**Figure 3**), with the majority falling into the hepatopancreatobiliary (HPB)-dominant disease, and systemic disease sub-groups.

Not IgG4-RD: 58 patients (37%) did not meet diagnostic criteria and were considered not to have IgG4-RD, with alternative diagnoses sought. These are listed in **Table S1**. Within this group the MDM identified 7 patients in whom malignancy was the likely diagnosis, and on this basis further investigations/therapy was planned. This included one patient with Inflammatory myelofibroblastic tumour; a disease that is well known to be challenging to differentiate histologically from IgG4-RD. Other notable non-IgG4-RD diagnoses include those patients with Vasculitis (6), Sarcoidosis (3), Crohn’s

disease (3), and Primary Sclerosing Cholangitis (4). In 16 cases the MDM felt there was not enough supportive evidence for a diagnosis of IgG4-RD but were unable to offer an alternative diagnosis.

Management advice

In all there were 206 MDM discussions of the 156 patients (**Figure S1**); 116 patients were given management advice.

For those patients with definite or possible IgG4-RD 61/97 had changes to their therapeutic strategy recommended as an outcome of the IgG4 MDM. There were 139 management discussions in 97 patients (**Figure 4**); in 80 (58%) of these recommendations were made to change treatment. The majority, 61/80 were escalations of therapy with 19 patients recommended for rituximab. Additional radiological imaging was recommended in 50 cases (36%) including FDG-CT-PET, MRCP, MRI Orbits and CT Chest/Abdomen/Pelvis, primarily to investigate sub-clinical organ involvement and/or assess treatment response. A targeted biopsy was recommended to assist diagnosis in 20 cases (14%), with sites identified based on radiological assessment. Additional specialist opinion was sought outside those present at the MDM in 12 cases (9%).

A small number of treatment recommendations were made for patients without a diagnosis of IgG4-RD (**Figure 4**). Primarily these involved stopping inappropriate therapy, particularly corticosteroids (6); or, in a few cases escalation of therapy (3), typically in active vasculitis. Where possible the MDM recommended appropriate imaging (11), biopsy (15) or onward referral (11).

Discussion

Our initial experience of delivering a supra-regional IgG4-RD MDM, reported here, is that it provides an invaluable forum in which to pool expertise to support diagnostic assessment and management. The surprising finding that the MDM was able to refute a suspected diagnosis of IgG4-RD in a third of cases highlights the importance of such a service. Additionally, the trend of increasing numbers of external referrals to the MDM likely demonstrates an increased awareness of IgG4-RD as a condition with commensurate increase in demand for diagnostic and management advice. This is further demonstrated by looking at referrals before and after the inaugural UK IgG4-

RD symposium, held in London in March 2018. The mean number of cases per MDM discussion prior to April 2018 was 6 rising to 13 between April 2018 and August 2019.

With increased awareness of the condition serum IgG4 testing is becoming more frequent, and yet interpretation of the result is key given the relatively low specificity of serum IgG4 as a diagnostic test. A number of inflammatory and malignant conditions can have an elevated serum IgG4, all of which are important clinical mimics of the disease.[11] Furthermore, we demonstrated that 23% of patients given a definite or possible diagnosis of IgG4-RD at MDM had a normal serum IgG4 level.

Referrals predominantly arose from pancreatobiliary medicine and hepatology. This reflects a speciality referral bias towards the founding clinicians of our MDM, but is also supported by recent published data sub-classifying clinical disease phenotypes in a multi-centre cohort, whereby the pancreas was the most frequent organ involved in IgG4-RD.[28] However, we demonstrated a broad coverage of all organs and specialities, incorporating cases from all four disease phenotypes (HPB, retroperitoneum and aorta, limited head and neck and systemic disease). Indeed, as a more diverse range of specialists have become involved with our service, more detailed imaging to detect sub-clinical disease is performed, and recognition of this rare disease increases, we have seen a steady increase in the number of head and neck, retroperitoneal and aortic referrals over the last year.

A particular diagnostic challenge relates to the 26% of new referrals in whom the condition was thought possible but did not meet diagnostic criteria and/or there was insufficient evidence (usually histology) to be certain of the diagnosis. Indeed, a common scenario in the group of ‘possible’ cases were those patients in whom retrospective review of their clinical case was highly consistent with IgG4-RD but who had received empirical treatment that rendered subsequent serological and histological results impossible to interpret. This highlights the importance of timely expert review with pre-treatment radiology, serology and histopathology to provide the best chance to reach an accurate diagnosis.

The data from our MDM emphasised the importance and challenge of differentiating IgG4-RD from malignancy. In our series, two patients had undergone life-changing treatment for presumed cancer, but a diagnosis of IgG4-RD was eventually reached on the retrospective examination of histology specimens. However IgG4-RD has also been associated with an increased risk of malignancy itself, meaning that malignancy

should still be actively excluded even in the context of a positive IgG4-RD diagnosis.[16,29,30] With broader clinician awareness of IgG4-RD it is also vital that an assumption of IgG4-RD is not made without firm diagnostic grounds, and the pooled expertise of the IgG4-RD MDT may help with this.

Once a diagnosis of IgG4-RD is made, treatment can be challenging. The morbidity associated with long-term steroid use is well known, yet data in IgG4-RD for steroid-sparing agents such as azathioprine is lacking, and, it is still not clearly defined which patients should receive maintenance treatment and with what. The intent of the MDM is to minimise corticosteroid-related harm and promote second-line immunomodulatory agents when necessary. The extensive therapeutic experience of rheumatologists within our MDM has been essential to establish this balance. Disease activity, specific organ 'urgency' and evidence of organ damage are important factors in deciding upon appropriate medication and treatment duration. Critically, previous clinical experience in managing patients with IgG4-RD often influenced MDT treatment decisions amongst our patients. Thus, faced with a lack of high-quality evidence to guide choice of therapeutics in a rare disease, the collective experience of the MDM becomes increasingly valuable. Furthermore, management of such cases within a specialist MDM facilitates the development of rare disease registries, such as that maintained by our service and aligned with the MDM, which will provide evidence to inform future decisions.

A particular management issue surrounds the use of rituximab, which was recommended for 19 patients following MDM discussion. This is a high cost treatment with which many gastroenterologists are unfamiliar, but rheumatologists and haematologists are often experienced. The multi-speciality involvement of the IgG4-RD MDM is well suited to advising on rituximab use, particularly in cases with HPB disease. It is imperative to ensure that the diagnosis is secure, and that due consideration has been given to all therapeutic options in order to ensure clinically appropriate and equitable access to this medication. In the UK the NHS has approved rituximab for IgG4-RD only in the setting of failed treatment or intolerance of first- and second-line therapies, and after approval through a specialist IgG4-RD MDM such as ours. Our MDM therefore provides an effective forum for patient selection, treatment supervision and monitoring of this treatment.

Conclusion

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IgG4-RD is a recently, but increasingly recognised multi-system disease which presents both diagnostic and therapeutic challenges for the non-specialist and specialist clinician. Through collective experience and multi-disciplinary decision an IgG4-RD MDM provides an invaluable forum for ensuring accurate diagnosis and consistency in management. In addition, we believe that patients have access to a wide range of specialist clinicians best placed to drive and implement research driven changes in diagnosis and management. We welcome new referrals at <https://igg4-rd.ndm.ox.ac.uk> .

For Review Only

Figure Legends:

Figure 1. Referral sources to the IgG4-RD Multidisciplinary Meeting. Referral by source comparing MDM host institutions to external referrals.

Figure 2. A. Proportional distribution of MDM referrals by region. B. UK map demonstrating geographic location of referral centres. Circles are proportional to referral numbers from each centre. C. Number of MDM case discussions by referring speciality.

Figure 3. A. MDM referrals by disease phenotype; black bars represent those referrals given a definite IgG4-RD diagnosis; pale grey, possible IgG4-RD diagnosis. B. Proportion of IgG4-RD diagnoses by disease phenotype.

Figure 4. MDM management recommendations for all 206 case discussions. 'IgG4-RD' includes those patients given definite or possible IgG4-RD diagnoses. Treatment demonstrates the proportion of patients in each group in which therapy was; escalated, black; de-escalated, pale-grey; or unchanged, dark grey,

Table S1. Alternative diagnoses offered at MDM for those patients without IgG4-RD.

Table S2. Differential diagnoses offered at MDM for those patients with possible IgG4-RD.

Figure S1: The number of MDM discussions per patient.

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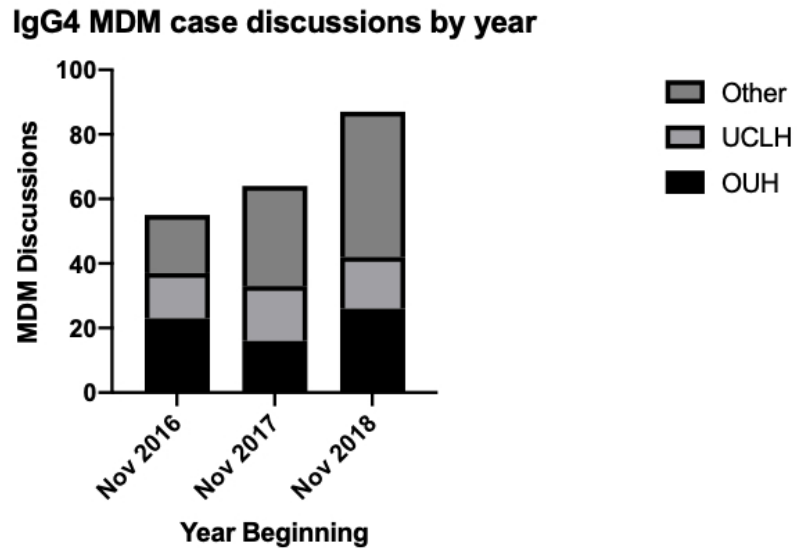


Figure 1

254x190mm (72 x 72 DPI)

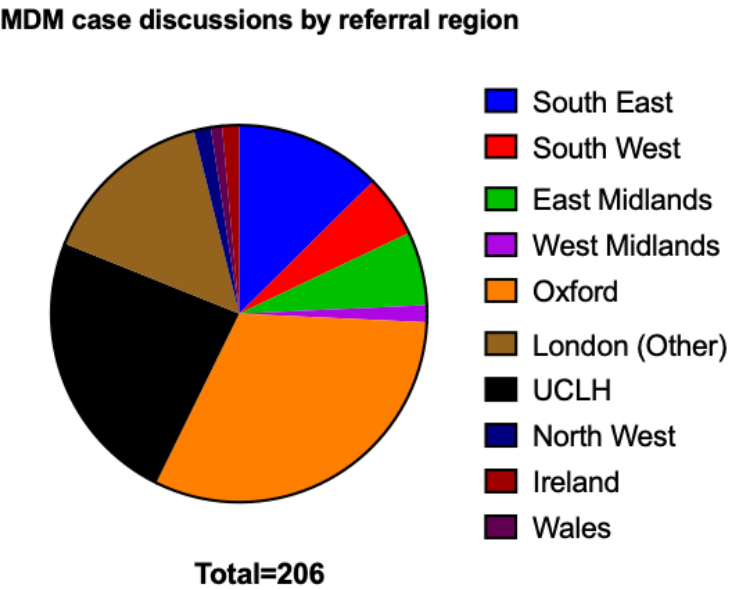


Figure 2A
254x190mm (72 x 72 DPI)



Figure 2B

162x111mm (96 x 96 DPI)

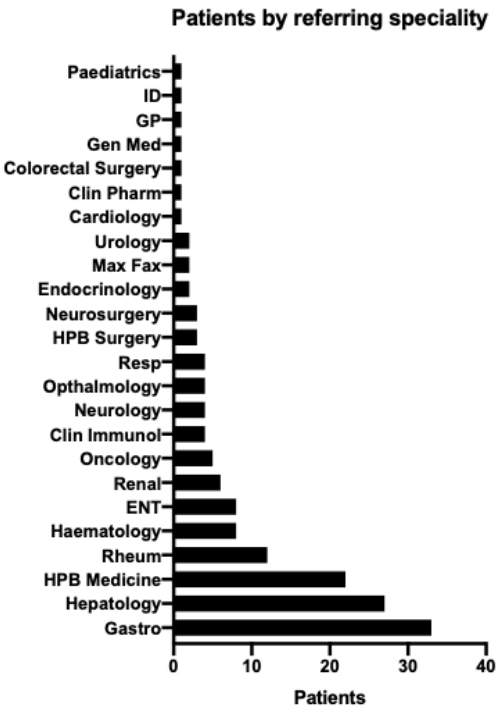


Figure 2C

254x190mm (72 x 72 DPI)

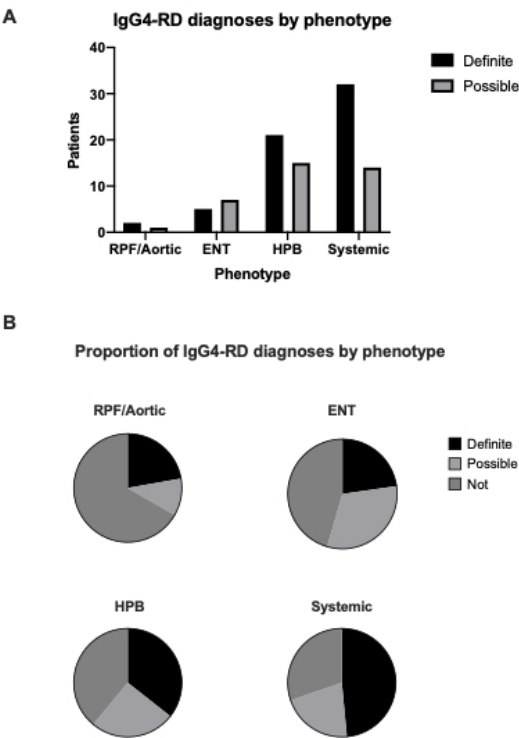


Figure 3A and B

254x190mm (72 x 72 DPI)

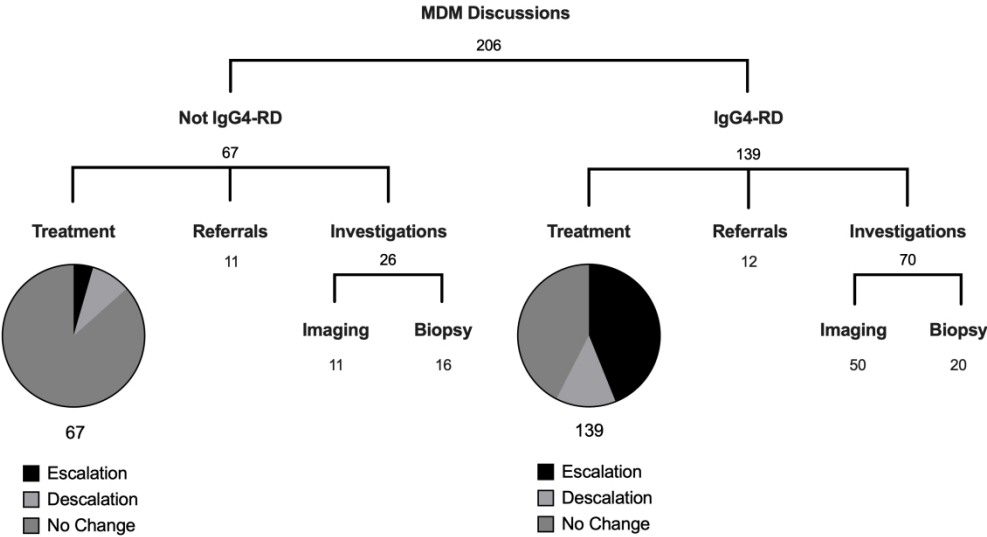


Figure 4

275x152mm (300 x 300 DPI)