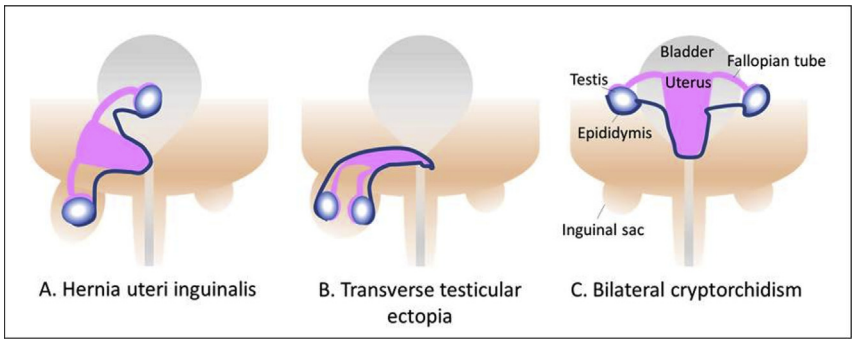

Fig. 2 The three different phenotypes of PMDS. (A) Hernia uteri inguinalis (unilateral cryptorchidism and inguinal hernia): unilateral undescended testis. The contralateral descended testis drags the Müllerian remnant down as inguinal hernia. (B) Transverse testicular ectopia: the descended testis drags down the Müllerian remnants together with the other testis on the same side. (C) Bilateral cryptorchidism: uterus in the pelvis, with bilateral testes embedded in the broad ligament.

The known pathogenic missense variant *AMHR2* c.1499G>A. p.(Cys500Tyr) causes substitution of cysteine to tyrosine at amino acid position 500 which is located at the intracellular domain of the AMH receptor and is frequently reported in PMDS patients.[1,2] The other nonsense variant *AMHR2* c.64C>T is a novel variant located in exon 2; the substitution of C to T nucleotide creates a premature stop codon at amino acid position 22 (p.Arg22*). This variant is extremely rare in normal controls (Exome Aggregation Consortium) and this is compatible with disease with autosomal recessive inheritance. *In silico* analysis by Mutation Taster and SIFT also predicts p.Arg22* as pathogenic.

In conclusion, an intra-operative finding of Müllerian duct remnants is diagnostic of PMDS, whereas serum AMH level is useful in differentiating the two types, and drives the genetic testing to either *AMH* gene or *AMHR2* gene. We present a case of type II PMDS with a novel nonsense variant (p.Arg22*) identified in *AMHR2*. Early surgical management is preferred to minimise the risk of malignant transformation of the intra-abdominal testes and Müllerian duct remnants, as well as to maximise the chance of preserving fertility.

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Concurrent anti-GBM disease and IgA glomerulonephritis

Sir,

A 22-year-old Caucasian male with a four pack-year history of smoking presented due to one month of recurrent, moderate volume haemoptysis and some dyspnoea. There was no history of recent flu-like illness or other infection. He had no other occupational or recreational exposures relevant to these respiratory symptoms. There was no other significant medical history, including no history of previously detected haematuria or proteinuria. At initial work-up haemoglobin was 90 g/L, serum creatinine 77 μmol/L and eGFR >90 mL/min. ESR was raised at 35 mm/hr. Chest X-ray showed bilateral lower lobe patchy heterogeneous parenchymal opacities. There were 250 dysmorphic erythrocytes in urine and 0.5 g per day of proteinuria.

Renal biopsy contained eleven glomeruli with one segmental necrotising lesion and two cellular crescents observed. The remaining glomeruli showed a mild and focal increase in mesangial cellularity. The tubules contained some luminal erythrocyte casts and no extraglomerular vasculitis was apparent. There was no interstitial fibrosis. Immunofluorescence demonstrated linear staining with IgG (Fig. 1A) and C3 along the glomerular basement membrane as well as prominent glomerular mesangial staining with IgA (Fig. 1B). Electron microscopy showed only the typical glomerular mesangial electron-dense deposits of IgA nephropathy.

At this point anti-GBM serology (ELISA for IgG autoantibodies against the NC1 domain of alpha-3 collagen chain) returned as positive. In addition, ANA and dsDNA antibodies were not elevated. Both an ENA screen and ANCA antibodies were also negative.

A final diagnosis of concurrent anti-GBM disease and IgA glomerulonephritis was made.

Treatment consisted of a fixed course of 21 sessions of plasma exchange. In addition, oral prednisolone was commenced at 75 mg daily, tapering to 10 mg daily at 4 months and with intention to cease at 6 months. Oral cyclophosphamide was also commenced at 150 mg daily. It was ceased at 2 months and replaced with oral azathioprine at 100 mg daily. The patient had resolution of clinical symptoms, with normalisation of haemoglobin and negative anti-GBM serology at 4-month follow-up. Serum creatinine remained within the normal range, however there had been a slight increase in proteinuria to 0.7 g per day.

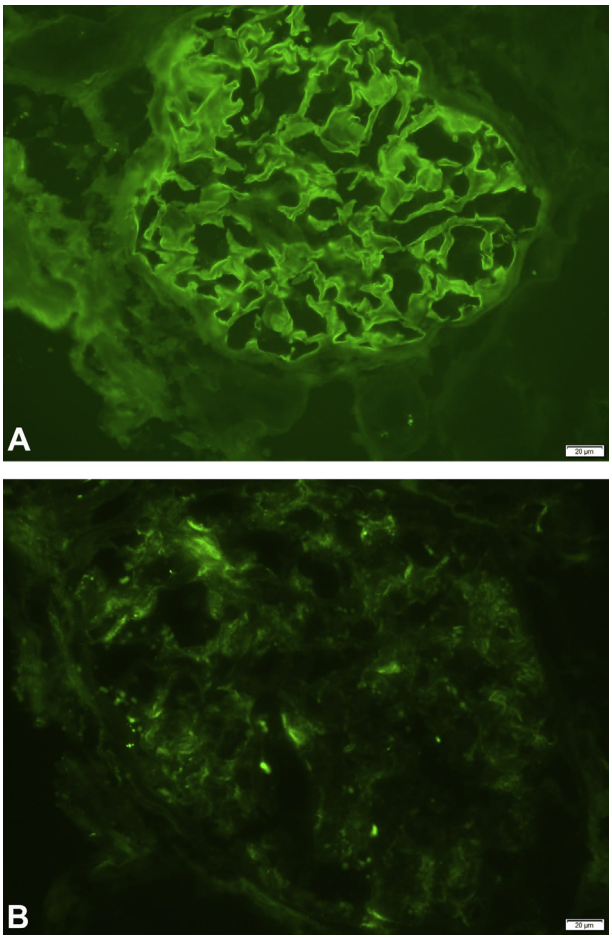

Fig. 1 (A) Linear positive immunofluorescence staining along the glomerular basement membrane for IgG. (B) Granular positive immunofluorescence staining in the glomerular mesangium for IgA.

Concurrent anti-GBM disease and ANCA-associated (pauci-immune) glomerulonephritis is a well-recognised phenomenon.[1] Concurrent anti-GBM disease and immune complex-mediated glomerulonephritis is less common but also described,[2] and amongst this group there are only four previous case reports that could be found in the literature of concurrent anti-GBM disease and IgA nephropathy.[3–6]

The current case presents some features of difference to the four cases referenced above.

Firstly, the current case involves a Caucasian patient, whereas previous reports involved Asian patients. When taken together, this may reflect the well-established disparity in prevalence of IgA nephropathy between European and Asian populations. This reported disparity[7] results in an Asian population prevalence of 30–60% versus a European population prevalence of 20–30%. Ethnic influences are highlighted when the North American population prevalence of 10% is subclassified, revealing a native North American prevalence of 38% and an African-American prevalence of 2%.[7] At the genetic level, genome-wide association studies (GWAS) have cumulatively found 15 loci for IgA nephritis susceptibility, studied and validated across populations of both Asian and European ethnicity.[7] Although the effects of some genes at these loci has been elucidated, (e.g., locus 1q32 coding for genetic variants in CFH, CFHR3 and CFHR1 that affect complement activation) the underlying genetic mechanism for the development of the clinical disease remains unknown.

Secondly, the current patient had haemoptysis and dyspnoea, respiratory features not present in the previous reports. Interestingly, in three of these reports the smoking status of the patient was not disclosed and in one report the patient was described as a non-smoker. Smoking status is known to be a crucial factor in determining the risk of pulmonary haemorrhage in the setting of anti-GBM disease,[8] and is the most likely explanation for the presence of respiratory symptoms in the current case.

Thirdly, the current patient had only 22% of glomeruli with crescents, well below the figure described in the other patients. As indicated above, he came to clinical attention as the result of one month of respiratory symptoms, in the absence of symptoms directly referable to the kidneys. The patients whose cases have previously been reported describe durations of illness between one week and two months prior to presentation.[3–6] Hence the relatively low number of glomerular crescents in this patient is not due to a particularly early clinical presentation, but rather due to his anti-GBM disease being slanted towards respiratory effects most likely as a result of smoking. Many patients with a respiratory-slanted presentation of anti-GBM disease have a history of smoking, a recent flu-like illness or other infection.[9] A minority have a history of hydrocarbon exposure.[10]

While a precise mechanistic interaction between IgA glomerulonephritis and anti-GBM disease remains undescribed, some reports put forth putative pathogenic relationships. There is a suggestion[3,5,6] that the deposition of immune complexes in glomeruli and the release of inflammatory mediators such as IL-1, TNF and IL-6 can induce conformational changes in the glomerular basement membrane. This leads to the exposure of cryptic antigen sites and immune response to the previously sequestered antigens, including the production of anti-glomerular basement membrane antibodies.

Abnormalities of IgA molecules in IgA glomerulonephritis may also serve as a link to the development of anti-GBM disease. A defect in galactosylation of IgA1, both in serum and in elution from nephrectomy specimens has been identified in patients with IgA glomerulonephritis.[2] Serum autoantibodies against this abnormal IgA1 were IgG2 subclass predominant. Some patients with anti-GBM disease combined with IgA glomerulonephritis demonstrated deposits of IgA1 with aberrant polysaccharide chain along the GBM and anti-GBM IgG2. It could thus be speculated that the deposition of the abnormal IgA1 along the GBM might lead to novel antigen formation and the production of the anti-GBM antibodies.[2]

In summary, this report substantiates the documented occurrence of anti-GBM disease in concert with IgA nephropathy. It also looks at some aspects of pathogenesis, and widens the clinical and histopathological spectrum of features described in conjunction with this phenomenon.

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NK-cell enteropathy, a potential diagnostic pitfall of intestinal lymphoproliferative disease

Sir,

NK-cell enteropathy is a rare and clinically indolent lymphoproliferative disorder involving the gastrointestinal tract. The disease, which is characterised by an atypical proliferation of CD56 expressing NK-cells within the mucosa, is a recently described unique clinicopathological entity which has also been coined 'lymphomatoid gastropathy'.[1] Patients experience a benign or indolent clinical course with persistent local disease or spontaneous regression punctuated by occasional relapses. Here, we present a case of NK-cell enteropathy which was diagnosed in an asymptomatic patient undergoing routine colonoscopic surveillance. Our case highlights the importance of recognising this entity in order to avoid misdiagnosis of an aggressive enteric NK/T cell lymphoma which would result in unnecessary treatment burden for the patient.

Our patient was an otherwise well 58-year-old man, referred for colonoscopic assessment due to anxiety about bowel cancer after a recent diagnosis in a friend. He denied any rectal bleeding or recent weight loss and his medical history was unremarkable. His family history was remarkable only for a maternal aunt who was diagnosed with bowel cancer in her mid-60s. Colonoscopy revealed a 10 mm semi-sessile polyp in the lower third of his rectum (Fig. 1) with abnormal submucosal vasculature. The endoscopic impression at the time was that of a solitary rectal ulcer. The polyp was snared and submitted for histological examination.

Haematoxylin and eosin (H&E) stained sections of rectal mucosa deep to submucosa revealed lamina propria expansion by a relatively monomorphous infiltrate of intermediate sized lymphoid cells with irregular nuclear borders, finely clumped nuclear chromatin, small indistinct nucleoli and moderate to abundant pale cytoplasm with a somewhat histiocytoid appearance (Fig. 2A). Some cells contained striking intracytoplasmic eosinophilic granules (Fig. 2B). Mitoses were inconspicuous and there was no necrosis. Epitheliotropism and intraepithelial lymphocytosis were not identified and there was no evidence of angiocentric or angiodestructive growth. The atypical lymphoid infiltrate formed variably sized nodular aggregates which were rimmed by small mature lymphocytes and a polymorphous population of inflammatory cells composed of eosinophils, plasma cells, and histiocytes. Scattered reactive lymphoid follicles were present in the adjacent mucosa.

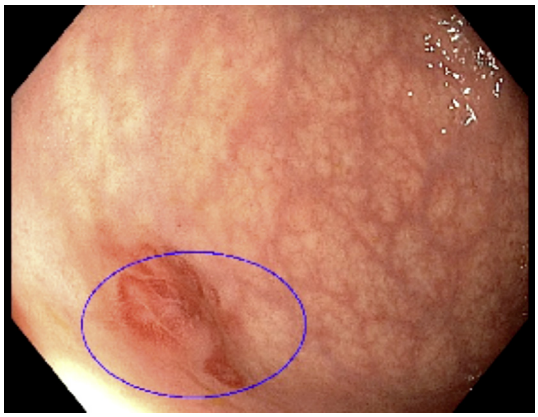

Fig. 1 Colonoscopic appearance of the semi-sessile rectal polyp with abnormal submucosal vasculature.

On immunohistochemistry, the atypical lymphoid cells showed strong diffuse cytoplasmic expression for CD45, CD56, granzyme B and cytotoxic granule-associated RNA binding protein TIA1 (Fig. 2C,D). There was variable expression for T-cell markers, with CD3 and CD7 detected, while CD4, CD5 and CD8 were absent. TCR-βF1 was negative, as was *in situ* hybridisation for EBV-RNA. CD20 highlighted the rim of small mature lymphocytes surrounding the atypical infiltrate as well as adjacent reactive lymphoid follicles with well formed germinal centres. Ki-67 proliferation index was low.

The immunophenotypic findings revealed an NK/T-cell lineage lymphoproliferative disease. We considered the possibility of an enteric NK/T cell lymphoma such as extranodal NK/T-cell lymphoma or monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL; previously called Type II enteropathy-associated T-cell lymphoma[2]); however, the absence of high grade features (e.g., tumour cell necrosis and apoptosis), lack of epitheliotropism and angiocentric/angiodestructive growth, and absence of detectable EBV-RNA, were incompatible with either diagnosis. Moreover epitheliotropism was not identified in the adjacent mucosa. The overall findings therefore were most in keeping with NK-cell enteropathy.

Following the diagnosis, the patient was referred to a haematologist and had full lymphoma workup, including a bone marrow biopsy, a staging CT scan of his chest, abdomen and pelvis, as well as a PET scan, which were all negative. He remained asymptomatic 6 months after the diagnosis (at the time of this case report).