Unusual association of diseases/symptoms

Familial granulomatosis with polyangiitis: three cases of this rare disorder in one Indoasian family carrying an identical HLA DPB1 allele

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Summary

The aetiology of granulomatosis with polyangiitis (GPA) remains unclear. There is likely a complex interplay between environmental triggers and genetic predisposition. Early diagnosis and treatment improve outcome in this condition with an untreated reported mortality of 90%. There are a few cases of familial GPA in the literature, but we report here the interesting and rare scenario of three members of the same Indoasian family with GPA who share an identical human leucocyte antigen (HLA) haplotype. In particular, all three members of the family share the HLADPB1 allele *04:01. This is the first reported Indoasian family with GPA. The HLA antigens found on genotyping our family and, in particular, HLADPB1 has been linked with GPA in previous studies. Genome-wide association studies in Anti Neutrophil Cytoplasm Antibody (ANCA) associated vasculitis (AAV) are currently in progress and should improve understanding of the genetic aspects of this disease. There may be important implications for patients with GPA and for their relatives.

BACKGROUND

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is a rare necrotising vasculitis with an incidence of approximately 10 cases per million population in the UK. It is a multisystem disorder often affecting the upper and lower respiratory tract and the kidneys, with a mortality of over 90% if untreated. Diagnosis is based on characteristic clinical and pathological findings, usually in association with antineutrophil cytoplasm antibody (ANCA) directed against neutrophil and monocyte proteinase 3 (PR3) or myeloperoxidase (MPO). Even with modern immunosuppression, there is a significant morbidity and mortality both as a result of the disease process itself and treatment with agents such as steroids and cyclophosphamide.

The aetiology of GPA remains unclear and current hypotheses are based on the notion of environmental triggers, frequently infectious, in genetically susceptible individuals. While familial aggregation has been reported in other autoimmune diseases, including rheumatoid arthritis¹ and systemic lupus erythematosus,² there are very few reported cases of clustering of GPA in families. There is an understandable concern from patients about the risk of disease in their close relatives and the question of whether they can be screened. We report the rare finding of two siblings from an Indoasian family diagnosed with GPA, and their father who is also likely to have suffered with this disease. They all shared a common human leucocyte antigen (HLA) haplotype and a common HLA-DPB1 allele suggesting a role for HLA genes in pathogenesis of the disease.

CASE PRESENTATION

Patient 1

A 33-year-old Indoasian businessman with previous Grave's thyroiditis presented with deafness, bleeding gums and nasal congestion and was diagnosed in India as having GPA. He was found to be ANCA positive with a cytoplasmic staining pattern and antibody reactivity to PR3. He was treated with oral corticosteroids and made a significant symptomatic improvement. Two years later he developed urinary abnormalities in the context of a nephritic syndrome, and renal biopsy demonstrated a pauci immune focal and segmental glomerulonephritis. He was started on high dose steroids and cyclophosphamide, then converted to maintenance treatment with oral prednisolone and azathioprine. He developed steroid-induced diabetes, treated initially with oral hypoglycaemic agents then insulin. His renal function remained stable for over 20 years, at which time his creatinine rose slowly in conjunction with a rise in PR3-ANCA. Repeat renal biopsy revealed 45% tubular atrophy and no evidence of active glomerular lesions. He died in India aged 62 years from probable cardiac failure preceded by tuberculous meningitis.

Patient 2

The patient's sister also presented at the age of 33 years with bilateral supraorbital pain, sinusitis, new onset hearing loss, nasal blockage and epistaxis. She underwent nasal biopsies which confirmed granulomatous inflammation and was found to be PR3-ANCA positive. A CT scan of her head demonstrated paranasal inflammatory tissue and bony

Figure 1 (A) Severe sinus disease in patient 2. (B) Pulmonary nodules with cavity in patient 2.

destruction of the nose (figure 1A). A diagnosis of GPA was made and she was treated with oral corticosteroids, on which she made a symptomatic improvement. She subsequently developed mastoiditis which was treated with local debridement and the introduction of azathioprine. She developed a lacrimal gland mass 2 years later which was biopsied and found to be consistent with GPA, suggesting disease relapse for which she was treated with oral cyclophosphamide and prednisolone. She subsequently became ANCA negative for the first time. Following reduction of immunosuppression she developed headaches and relapsing sinus disease. Immunosuppression was recommenced with prednisolone and azathioprine. She went on to develop pulmonary nodules (figure 1B) for which methotrexate was substituted for azathioprine. At no stage during follow-up did she develop any renal abnormalities. She remains well aged 61 years.

Patient 3

The patients' father who lived in India developed sinus disease in his thirties. He underwent sinus biopsies, but the results are not available to us. He subsequently developed renal failure at the age of 40 years and following a renal biopsy in the UK, he was diagnosed with a rapidly progressive glomerulonephritis (RPGN). ANCA testing had not been introduced at that time but a diagnosis of GPA seems likely. He received a live related renal transplant from his brother and was maintained on azathioprine and prednisolone. His clinical course was complicated by tuberculosis and gout, but he was not reported to have

experienced any features of GPA. He died in India in his 60s, but the cause of death is unknown.

DISCUSSION

Our reported family is extremely rare, with two siblings both of whom presented at age 33 years with severe ear, nose and throat (ENT) symptoms. They were both found to be PR3-ANCA positive and were diagnosed with GPA. One sibling subsequently developed renal involvement while the other developed lung disease. Their father also presented with ENT symptoms in his 30s and developed renal failure due to RPGN, treated by renal transplantation. They shared a remarkably similar disease phenotype. HLA typing demonstrated a common haplotype: HLA-A 68, B44, Cw7, DR 17, 52 and DQ2 (table 1). The patients also shared the allele HLA-DPB1*0401. There are very few reported cases of familial clustering of GPA and none in Indoasian families. These include a case report of two sisters with GPA who both presented with nasal disease,³ and a family of eight siblings from Denmark, of whom two had a diagnosis of GPA.⁴ In the latter study, genotyping was performed but no HLA association was found between the siblings. In addition, Hay *et al*⁵ reported a brother and sister with GPA both with renal manifestations, and Gomes *et al*⁶ described the case of siblings who presented at the ages of 59 and 72 years with pulmonary and renal involvement. Gomes *et al*⁶ also reported the cases of a father and daughter with GPA who presented with renal disease. In a large population-based study, Knight *et al*⁷ found that only 2 of 6670 first-degree relatives of patients with GPA and 13 of 68 994 population controls contracted the disease, giving a relative risk of 1.56 (95% CI 0.35 to 6.90).

Genetic factors have been found to play an important role in GPA. These include associations with major histocompatibility complex (MHC) variants, as well as polymorphisms in genes encoding various proteins including α -1 antitrypsin and cytotoxic T lymphocyte antigen4 (CTLA4).⁸ The MHC loci found to have an association with GPA include HLA-DR2⁹ and DR8¹⁰ as well as HLA-DQw7, HLA-DR3, HLA-DR1 and HLA-DR9.⁸ The extended haplotype DPB1*0401/RxRB03, in particular, has been shown to have an extremely strong association with GPA (OR=6.41, $p=7.13 \times 10^{-17}$).¹¹ The single-nucleotide polymorphism (SNP) 3' of HLA-DPB1 has been shown to be highly associated with GPA ($p=6.4 \times 10^{-8}$).¹² Stassen *et al*¹³ studied 304 Dutch patients with GPA and found an association of HLA-DR4 with GPA, as well as with Anti Neutrophil Cytoplasm Antibody (ANCA) associated vasculitis (AAV) in general.

A variety of studies have suggested that production of PR3, the main target antigen in GPA, is also genetically determined, and that variations in expression of the

Table 1 HLA typing of the three patients

	HLA-A	HLA-B	HLA-C	HLR-DR	HLA-DQ	HLA-DPB1
Father	24,68	B-44,35	CW4,7	10,17,52	2,5	*04:01
Son	24,68	18,44	CW7,1203	17,11,52	2,7	*04:01
Daughter	11,68	7,44	CW5,7	17,53	2	*04:01

HLA, human leucocyte antigen.

PRTN3 gene which encodes PR3 can thus influence susceptibility to disease.¹⁴ The precise polymorphisms which result in this variation have not yet been determined; however, a number of SNPs have been identified in both its promoter and exonic sequences.¹⁵ α -1 Antitrypsin is a protease and functions as the main inhibitor of PR3. Various polymorphisms in the α -1 antitrypsin gene have been found to result in reduced function of the α -1 antitrypsin molecule and thus increased susceptibility to the damaging effects of PR3. In particular, the presence of the Z allele has been linked to (GPA).^{16 17} PTPN22 is a gene which encodes the protein tyrosine phosphatase non-receptor type 22. An association has been made between the 622 allele of this gene and GPA.¹⁸ Polymorphisms in CTLA4 have been associated with many autoimmune diseases including GPA.^{19 20}

This is the first case report of a family with GPA carrying an identical HLA haplotype and the first report of an Indoasian family with this disease. The HLA antigen found on genotyping our family have not been found to be associated with GPA in previous studies. Genome wide association studies in AAV are currently in progress and should increase understanding of the genetic aspects of this disease. There may be important implications for patients with GPA and their relatives. Since submission of this article, results of the genome wide association study in systemic vasculitis have now been published.²¹ This study has confirmed previous reports of the association of HLA DPB1 with GPA

Learning points

- The pathogenesis of granulomatosis with polyangiitis (GPA) remains to be fully elucidated and is thought to involve a complex interplay between environmental factors in genetically susceptible individuals.
- There may be important implications for relatives of patients with this disease.
- The human genome project will increase understanding of the genetics of GPA.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Klareskog L**, Stolt P, Lundberg K, *et al.* A new model for an aetiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reaction to autoantigens modified by citrullination. *Arthritis Rheum* 2006;(54):38–46.
2. **Rhodes B**, Vyse T. The genetics of SLE: an update in the light of genome wide association studies. *Rheumatology* 2008;(47):1603–11.
3. **Muniain M**, Moreno J, Gonzalez R, *et al.* Wegeners granulomatosis in two sisters. *Ann Rheum Dis* 1986;(45):417–21.
4. **Knudsen B**, Joergensen T, Munch-Jensen B. Wegeners granulomatosis in a family. *Scand J Rheumatol* 1988;(17):225–7.
5. **Hay E**, Beaman M, Ralston A, *et al.* Wegeners granulomatosis occurring in siblings. *Br J Rheumatol* 1991;**30**:44–145.
6. **Gomes A**, Nery F, Ventura A, *et al.* Familial clustering of ANCA small-vessel vasculitis. *NDT Plus*, 2009;(2):34–5.
7. **Knight A**, Sandin S, Askling J. Risks and relative risks of Wegeners granulomatosis among close relatives of patients with the disease. *Arthritis Rheum* 2008;**58**:302–7.
8. **Willcocks L**, Lyons P, Rees A, *et al.* The contribution of genetic variation and infection to the pathogenesis of ANCA associated vasculitis. *Arthritis Res Ther* 2010;(12):202.
9. **Elkon K**, Sutherland D, Rees A, *et al.* Brief report: HLA-antigen frequencies in systemic vasculitis: increase in HLA-antigen frequencies in systemic vasculitis: increase in HLA-DR2 in Wegeners granulomatosis. *Arthritis Rheum* 1983;(26):102–5.
10. **Katz P**, Alling D, Haynes B, *et al.* Association of Wegeners granulomatosis with HLA B8. *Clin Immunol Immunopathol* 1979;(14):268–70.
11. **Jagiello P**, Gencik M, Arning L, *et al.* New genomic region for Wegener's granulomatosis as revealed by an extended association screen with 1202 apoptosis related genes. *Hum Genet* 2004;(114):468–77.
12. **Heckmann M**, Holle J, Arning L, *et al.* The Wegener's granulomatosis quantitative trait locus on chromosome 6p21.3 as characterised by tagSNP genotyping. *Ann Rheum Dis* 2008;(67):972–9.
13. **Stassen P**, Cohen-Tervaert J, Lems S, *et al.* HLA-DR4, DR13(6) and the ancestral haplotype A1B8DR3 are associated with ANCA-associated vasculitis and Wegeners granulomatosis. *Rheumatology* 2009;(48):622–5.
14. **Schrieber A**, Busjahn A, Luft F, *et al.* Membrane expression of proteinase 3 is genetically determined. *J Am Soc Nephrol* 2003;(14):68–75.
15. **Gencik M**, Meller S, Borgmann S, *et al.* Proteinase 3 gene polymorphisms and Wegener's granulomatosis. *Kidney Int* 2000;(58):2473–7.
16. **Esnault V**, Testa A, Aucrain M, *et al.* Alpha 1 antitrypsin genetic polymorphism in ANCA positive systemic vasculitis. *Kidney Int* 1993;(43):1329–2.
17. **Griffith M**, Lovegrove J, Gaskin G, *et al.* C-antineutrophil cytoplasmic antibody positivity in vasculitis patients is associated with the Z allele of alpha-1-antitrypsin, and P-antineutrophil cytoplasmic antibody positivity with the S allele. *Nephrol Dial Transplant* 1996;(11):438–43.
18. **Jagiello P**, Aries P, Arning L, *et al.* The PTPN22 620 allele is a risk factor for Wegeners granulomatosis. *Arthritis Rheum* 2005;(52):4039–43.
19. **Giscombe R**, Wang X, Huang D. Coding sequence 1 and promoter single nucleotide polymorphisms in the CTLA 4 gene in Wegeners granulomatosis. *J Rheumatol* 2002;(29):950–3.
20. **Kamesh L**, Heward J, Williams J, *et al.* CT60 and +49 polymorphisms of CTLA 4 are associated with ANCA-positive small vessel vasculitis. *Rheumatology* 2009;(48):1502–5.
21. **Lyons PA**, Rayner TF, Trivedi S, *et al.* Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med* 2012;**367**:214–23.

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