When Autoimmune Diseases hide human inborn errors of immunity

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ABSTRACT

Autoimmune diseases are increasingly prevalent, often resulting from a complex interplay of genetic and environmental factors. Distinguishing between classical autoimmune disorders and primary immune regulatory disorders (PIRDs), a subgroup of human inborn errors of immunity (HIEI), can be challenging due to overlapping clinical features. We hereby report the case of a 32-year-old Caucasian male diagnosed with IgG4-related disease (IgG4-RD), Hashimoto's thyroiditis, and Autoimmune Lymphoproliferative Syndrome (ALPS), a HIEI characterized by defective lymphocyte apoptosis, lymphoproliferation, and autoimmunity. While most HIEI diagnoses occur in childhood, adult-onset presentations and co-occurring autoimmune conditions can obscure the clinical picture. Thorough patient history review, comprehensive laboratory workups and genetic testing are crucial for accurate diagnosis.

Kay words: *autoimmunity, Human Inborn Errors of Immunity, IgG4-related disease*

CASE PRESENTATION

We present the case of a 32 year-old Caucasian male with a complex history of immune activation. In 2015 he developed bilateral orbital pseudotumor. A Magnetic Resonance Imaging showed thickened and contrast-enhanced lacrimal glands. Biopsy of the glands revealed polyclonal B and T cell infiltration and more than 70 IgG4+ plasma cells per high power field. Blood tests showed elevated C-reactive protein (CRP) (54 mg/L, r.v. <6 mg/L), erythrocyte sedimentation rate (ESR) (32 mm/h, r.v. <15 mm/h), and IgG4 concentrations (3370 mg/L, r.v. <864 mg/L), along with negative antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), antineutrophil cytoplasmic antibodies (ANCA), within-range C3 and C4 concentrations, IgG1, IgG2, and IgG3 plasma concentrations. A diagnosis of IgG4-related disease (IgG4RD) was made based on histological and laboratory features. The patient initiated a high dose steroid treatment with complete resolution of the orbital pseudotumor.

A few months later, the patient started complaining of persistent low-grade fever, sweating, and diffuse, pruriginous maculopapular erythematous lesions. Soon after he was hospitalized for Streptococcal pneumonia soon after. Serum protein electrophoresis revealed profound hypogammaglobulinemia and, after exclusion of alternative causes, a diagnosis of common variable immunodeficiency was made. Treatment with intravenous immunoglobulins was started and weekly subcutaneous immunoglobulin injections were prescribed.

In January 2024 the patient presented to our outpatient rheumatology clinic complaining of orbital swelling, nasal obstruction, anosmia, ageusia, arthralgias, and erythematous, hyperkeratotic lesions on the dorsal surface of his hands upon glucocorticoids withdrawal. Blood tests showed elevated ESR (53 mm/h), CRP (51 mg/L), ALT (53 U/L, r.i. 6-41 U/L), AST (52 U/L, r.i. 5-33 U/L) bilirubin (total 42 mmol/L, r.v. <17 mmol/L; conjugated 10 mmol/L, r.v. <5 mmol/L; unconjugated 31 mmol/L, r.v <12 mmol/L), lactate dehydrogensase (LDH) 273 U/L, r.i. 125-220 U/L), IgE (129 IU/mL, r.i <100 IU/mL), and IgG4 (2.8 g/L, r.v. <0.8 g/L).

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Total IgG, IgG1, IgG2, IgG3, IgA, and IgM were within the reference intervals. Hepatitis B antibody concentration was measured and found to be low despite the patient having been vaccinated. ^{18}Fluorodeoxyglucose positron emission tomography (PET) scan revealed modest contrast uptake of the paranasal sinuses, parotid glands, latero-cervical and mediastinal lymph nodes, thymus, and thyroid gland. Multiple contrast enhanced exophytic renal lesions and a nodular region of the pancreatic head were detected as well. The patient was hospitalized for further diagnostic testing. Thyroid ultrasonography revealed an enlarged thyroid gland with small diffuse hypoechoic areas, likely representing inflammatory infiltrates. Blood tests revealed elevated anti-thyroid peroxidase (TPO) antibodies (187 IU/mL, r.v. <34 IU/mL), borderline anti-Thyroglobulin (TG) antibodies (115 IU/mL, r.v. <115 IU/mL), negative anti-thyroid-stimulating hormone receptor (TSH-R) antibodies, within-range TSH and Free Thyroxine (FT4). Immunophenotyping showed elevated CD3+CD4-CD8- T cells (1.8% of total lymphocytes, r.v. <1.5%; 2.6% of CD3+ cells, r.v. <2.5%). A diagnosis of Autoimmune Lymphoproliferative Syndrome (ALPS) was made based on available diagnostic criteria (1). Endoscopic ultrasound-guided biopsy of the pancreatic head revealed diffuse lymphocytic infiltration. Computed tomography scan-guided biopsy of the renal lesions showed tubulo-interstitial nephritis, a marked lymphoplasmacytic infiltrate rich in IgG4+ plasma cells (>50 IgG4+ plasma cells per high power field), with an IgG4+ to IgG+ plasma cell ratio >40%, findings diagnostic for IgG4-related disease. Blood sample was sent for whole exome sequencing but it was not possible to identify any germline mutation in an extended established panel of human inborn errors of immunity (HIEI) genes (2).

High dose steroid treatment was started and rituximab (two 1-gram intravenous infusions 15 days apart) was administered with resolution of the orbital pseudotumor and nasal obstruction. A follow-up PET scan has been scheduled to evaluate the radiological response of the renal and pancreatic lesions.

DISCUSSION

Autoimmune diseases are a common cause of medical concern, with a slowly but steadily increasing prevalence (3). They are generally caused by a complex interplay of polygenic genetic risk factors and environmental factors, and apparently exhibit contrasting features with immune-deficiency (4). Rising evidence reveals that they can rarely be a manifestation of a subgroup of HIEI known as primary immune regulatory disorders (PIRDs). Since the clinical presentation of classical autoimmune disorders can overlap with that of PIRDs-related autoimmunity, diagnosis may be difficult and require in-depth immunological testing.

This is a complex case of a patient diagnosed with ALPS, a HIEI, co-occurring with two autoimmune conditions: IgG4-RD and Hashimoto's thyroiditis. ALPS is a rare genetic disorder of defective lymphocyte apoptosis characterized by chronic lymphadenopathy, splenomegaly, autoimmune cytopenia, and evidence of non-malignant expansion of "double negative" CD4-CD8- T cells (5).

Historically, the disease was thought to be driven most commonly by heterozygous dominant-negative mutations in the *FAS* gene, and less frequently by homozygous loss of function mutations in *FAS*, heterozygous mutations of *FAS* ligand, *CASP10*, and *FADD*, and homozygous mutations of *CASP8* (5). However, recent studies have described an ALPS-like disease caused by somatic mutations of RAS and CTLA-4/LRBA deficiency (6).

Up to 72% of ALPS patients develop autoimmune conditions by the age of 30. Among most common associated autoimmune diseases, we find autoimmune hemolytic anemia and thrombocytopenia, autoimmune hepatitis, glomerulonephritis, uveitis, Guillain-Barre syndrome, aplastic anemia, vasculitis, pancreatitis, angioedema and alopecia (7,8). IgG4-RD, a systemic immune-mediated disorder characterized by mass-forming lesions in various organ systems and a tissue lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, has been previously described co-existing with ALPS in only three cases, while there are no reported cases of ALPS-related Hashimoto's thyroiditis, although the latter has been associated with single nucleotide polymorphisms (SNPs) in FAS (9).

Although most patients are diagnosed with inborn errors of immunity during childhood, incomplete penetrance and variable expressivity may lead to atypical adult-onset presentations, which may delay the diagnosis (2). "Epidemic" autoimmune diseases co-occurrence may further cloud the clinical picture, often making a correct diagnosis of HIEI extremely difficult. It is thus of fundamental importance to perform an in-depth laboratory workup when clinical suspicion of a primary immune regulatory disorder exists. Since inborn errors of immunity are often due to single-gene mutations in coding regions of the genome, genetic testing is necessary to make a definite diagnosis. However, widely- and rapidly-available blood tests can represent valuable diagnostic tools as well.

According to the 2022 update of the Classification of Human Inborn Errors of Immunity from the International Union of Immunological Societies Expert Committee, HIEI can be categorized into 10 groups according to the specific type of immune defect, whether it being in innate immunity, adaptive immunity, or immune regulation (10). Despite each group being characterized by specific laboratory findings mirroring the underlying immune defect, baseline tests should include routine complete blood count with differential together with a peripheral blood smear to screen for gross hematologic abnormalities, renal and liver function tests, inflammatory markers, and an infectious disease screening comprehensive of HIV testing. Depending on the type of immune defect suspected, different tests should be ordered. Innate immunity defects are generally assessed by measuring serum complement C3 and C4 plasma concentrations, complement activity assays, and neutrophil functional assays, whereas flaws in adaptive immunity can be detected by peripheral blood flow cytometry staining for CD3, CD4, CD19, CD20, and

Table 1
Steps for diagnosing an immune deficiency

Initial Clinical Assessment:
- Review patient history in detail, focusing on the frequency and severity of infections, presence of opportunistic infections, response to antimicrobial treatments, and any concomitant autoimmune conditions.
- Conduct a thorough physical examination.

Basic Laboratory Testing:
- Complete Blood Count (CBC) with differential: assess for any gross hematologic abnormalities.
- Peripheral Blood Smear: examine for abnormal cell morphology.
- Inflammatory Markers: measure Erythrocyte Sedimentation Rate and C-Reactive Protein.
- Renal and Liver Function Tests.
- Infectious Disease Screening: include comprehensive testing for common pathogens, including HIV.

Innate Immunity Defects:
- Serum Complement Concentration: test C3 and C4 plasma/serum concentration.
- Complement Activity Assays: perform CH50 and AH50 assays.
- Neutrophil Functional Assays: conduct Dihydrorhodamine (DHR) test or Nitroblue Tetrazolium (NBT) test.

Adaptive Immunity Defects:
- Peripheral Blood Flow Cytometry: assess CD3, CD4, CD19, CD20, and CD56 markers to identify T cells, B cells, and NK cells.
- T Cell Memory Panels: evaluate CD45RA and CCR7 markers.
- Lymphocyte Functional Assays: perform a Quantiferon test for T cell function.
- Plasma/Serum Immunoglobulin Testing: measure total IgGs, IgG subclasses, IgA, IgM, and IgE concentrations.
- Antibodies to Vaccine Antigens: evaluate antibody concentration before and after vaccination to assess B cell response.
- B Cell Memory Panels: test for CD27 and IgD markers.

Advanced Testing:
- Cytokine Measurements: measure plasma/serum concentration of cytokines such as IL-2, IL-6, IL-10, and Tumor necrosis factor (TNF)-alpha.
- Cytokine Receptor Concentration: assess serum concentration of soluble IL-2 receptor (sIL-2R) and TNF receptors (TNFR).
- Anti-Cytokine Antibody Assays: detect antibodies against cytokines, e.g., anti-Interferon (IFN)-gamma and anti-IL-17 antibodies.

Genetic Testing:
- If clinical suspicion of an inborn error of immunity is high, perform genetic testing such as whole exome sequencing to identify any relevant mutations.

Consultation and Collaboration:
- Engage with specialists in immunology, rheumatology, and genetics for comprehensive case evaluation and interpretation of results.
- Ensure close collaboration between medical laboratory scientists and medical doctors to facilitate a rapid and accurate diagnosis.

Treatment Considerations:
- Start treatment based on the specific diagnosis, which may include immunoglobulin replacement therapy, corticosteroids, or other immunosuppressive treatments.
- Regularly monitor the patient's response to treatment and adjust as necessary.

Follow-Up:
- Schedule regular follow-ups to monitor disease progression, treatment efficacy, and any potential complications.

CD56, thereby identifying T cells, B cells, and natural killer cells. When a T cell or combined immunodeficiency is suspected, further testing should include T cell memory panels, staining for CD45RA and CCR7, and lymphocyte functional assays including, for instance, a quantiferon test as a surrogate of T cell mitogen induced activation. Alternatively, B cell and antibody deficiencies should be evaluated by means of serum immunoglobulin testing (including total IgGs and subclasses, IgA, IgM, and IgE), antibody concentrations to vaccine antigens, and B cell memory panels. Efficient B cell response can be also assessed by measuring antibody concentration before and after a specific vaccination. Lastly, advanced, second-level testing may include measurement of cytokines and cytokine receptor concentrations, and anti-cytokine antibody assays (11) (Table 1). Of note, these tests should be performed off immunosuppressive treatment to avoid possible confounding factors that could interfere with results interpretation.

Primary immune regulation disorders' diagnosis may seem an extremely arduous task. A thorough review of the patient's history is fundamental; the patient should be specifically asked about frequency and severity of infections, development of opportunistic infections, and response to antimicrobial treatments, and should also be assessed for concomitant autoimmune conditions. When clinical suspicion of a HIEI arises, common and inexpensive laboratory tests can provide important clues to reach the correct diagnosis. Therefore, close collaboration between medical laboratory scientists and medical doctors is instrumental to provide a rapid and correct diagnosis of these complex disorders.

CONFLICT OF INTEREST

None

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