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Approach to Adult-Onset Inborn Errors of Immunity: Defining the Enigma

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Introduction

Inborn errors of immunity (IEI), formerly known as Primary immunodeficiency Disorders (PIDs), are a diverse group of inherited disorders resulting from defects in the development or function of the immune system[1]. Advances in molecular genetics and immunology have significantly expanded the understanding of these conditions, leading to the identification of more than 500 distinct disorders caused by mutations in over 450 genes[2]. The term 'Inborn Errors of Immunity' was adopted by the International Union of Immunological Societies (IUIS) to reflect the broad spectrum of clinical manifestations beyond susceptibility to infections[3].

Traditionally, IEIs were considered rare disorders characterised primarily by recurrent, severe, or unusual infections. However, growing evidence has demonstrated that many patients also present with immune dysregulation, autoimmunity, autoinflammation, allergy, lymphoproliferation, and malignancy[2,4]. Consequently, the clinical spectrum of IEIs is much wider than previously recognised, often leading to delayed diagnosis and increased morbidity.

Early recognition and diagnosis of IEIs is crucial because timely interventions, including immunoglobulin replacement therapy, antimicrobial prophylaxis, hematopoietic stem cell transplantation, and targeted molecular therapies, can significantly improve patient outcomes and quality-of-life[3].

Prevalence

The prevalence of IEIs varies across regions worldwide and is influenced by factors such as genetic background, consanguinity, healthcare professionals' awareness, and the availability of diagnostic facilities. Improved awareness, newborn screening programs, advanced immunological testing, and next-generation sequencing technologies have contributed to a steady increase in the number of diagnosed cases worldwide.

Population-based registries from Europe and North America have reported prevalence rates ranging from approximately 2.7 to 11 cases per 100,000 population[5]. The prevalence documented in national registries varies according to diagnostic capabilities and reporting systems. France has reported a prevalence of approximately 11 per 100,000 population, while the United Kingdom and Germany reported 5.9 per 100,000 and 2.7 per 100,000 population, respectively[5,6]. Common Variable Immunodeficiency (CVID) represents the most frequently diagnosed IEI in adults, whereas severe combined immunodeficiency (SCID) and combined immunodeficiencies are more commonly identified in the pediatric population.

The true prevalence in India remains uncertain and is believed to be significantly underestimated because of limited awareness, inadequate diagnostic infrastructure, and restricted access to genetic testing. Data from tertiary care centers and the Indian Society for Primary Immunodeficiency (ISPID) registry suggest a steadily increasing number of diagnosed cases over the last decade. Predominantly, antibody deficiencies, combined immunodeficiencies, and phagocytic defects constitute the majority of reported cases. Compared with Western countries, India reports a relatively higher proportion of severe combined immunodeficiencies and autosomal recessive disorders, partly due to higher rates of consanguinity in certain regions. Recent estimates suggest that tens of thousands of patients with IEI may remain undiagnosed across the country[7].

Classification of Inborn Errors of Immunity (IEI)

The International Union of Immunological Societies (IUIS) classifies Inborn Errors of Immunity[3] into the following major categories:-

1. Immunodeficiencies Affecting Cellular and Humoral Immunity: These disorders involve defects in both T-cell and B-cell immunity, leading to severe susceptibility to infections. Examples: Severe Combined Immunodeficiency, MHC class II deficiency.
2. Combined Immunodeficiencies with Associated or Syndromic Features: These disorders are characterised

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by immunodeficiency accompanied by developmental abnormalities or syndromic manifestations. Examples: Wiskott-Aldrich syndrome, Ataxia-telangiectasia, DiGeorge syndrome, Hyper-IgE syndrome.

3. Predominantly Antibody Deficiencies: The most common group of IEIs, characterised by impaired antibody production. Examples: Common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Selective IgA deficiency, Hyper-IgM syndrome.

4. Diseases of Immune Dysregulation: These disorders result from defects in immune tolerance and regulation, leading to autoimmunity and lymphoproliferation. Examples: Autoimmune Lymphoproliferative Syndrome (ALPS), Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) IPEX syndrome, CTLA4 deficiency, and LRBA deficiency.

5. Congenital Defects of Phagocyte Number or Function: Characterised by impaired neutrophil production or function resulting in recurrent bacterial and fungal infections. Examples: Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), Severe Congenital Neutropenia.

6. Defects in Intrinsic and Innate Immunity: These disorders predispose individuals to specific pathogens because of defects in innate immune pathways. Examples: MyD88 deficiency, IRAK4 deficiency, Chronic Mucocutaneous Candidiasis.

7. Autoinflammatory Diseases: Characterised by recurrent episodes of sterile inflammation due to dysregulation of the innate immune system. Examples: Familial Mediterranean Fever (FMF).

8. Complement Deficiencies: Caused by defects in complement proteins, leading to recurrent infections and autoimmune diseases. Examples: C2 deficiency, C3 deficiency, Terminal complement component deficiencies (C5 - C9).

9. Bone Marrow Failure Syndromes: Characterised by defective hematopoiesis and variable immunodeficiency. Examples: Fanconi anaemia, Dyskeratosis congenita, Shwachman-Diamond syndrome.

10. Phenocopies of Inborn Errors of Immunity: Conditions that clinically resemble IEIs but result from acquired genetic alterations or autoantibodies. Examples: Autoantibodies against IFN-γ.

Genetic Mutations Associated with Major Subtypes of Inborn Errors of Immunity

1. Immunodeficiencies Affecting Cellular and Humoral Immunity	
Disease	**Gene Mutation**
X-linked SCID	IL2RG
ADA deficiency SCID	ADA
JAK3 deficiency	JAK3
RAG deficiency	RAG1, RAG2
MHC class ii deficiency	RFZANK, RFX5
2. Combined Immunodeficiencies with Associated or Syndromic Features	
Disease	**Gene Mutation**
Wiskott-Aldrich syndrome	WAS
Ataxia-telangiectasia	ATM
DiGeorge syndrome	22q11.2 deletion
Hyper-IgE syndrome	STAT3
3. Predominantly Antibody Deficiencies	
Disease	Gene Mutation
X-linked agammaglobulinemia	BTK
Common Variable Immunodeficiency	TNFRSF13B, NFKB1, NFKB2
Selective IgA deficiency	Multiple susceptibility loci (often sporadic)
Hyper-IgM syndrome	CD40LG, CD40, AICDA
4. Disease of Immune Dysregulation	
Disease	**Gene Mutation**
ALPS	FAS, FASLG
IPEX syndrome	FOXP3
CTLA4 deficiency	CTLA4
LRBA deficiency	LRBA
5. Congenital Defects of Phagocyte Number or Function	
Disease	**Gene Mutation**
Chronic Granulomatous Disease	CYBB, CYBA, NCF1
Leukocyte adhesion deficiency type i	ITGB2
Severe congenital neutropenia	ELANE, HAX1
6. Defects in Intrinsic and Innate Immunity	
Disease	**Gene Mutation**
MyD88 deficiency	MYD88
IRAL4 deficiency	IRAK4
Chronic mucocutaneous candidiasis	STAT1 GOF
7. Autoinflammatory Diseases	
Disease	**Gene mutation**

Familial Mediterranean Fever	MEFV
CAPS	NLRP3
TRAPS	TNFRSF1A
8. Complement Deficiencies	
Disease	**Gene mutation**
C2 deficiency	C2
C3 deficiency	C3
Terminal complement deficiency	C5 – C9
9. Bone Marrow Failure Syndromes	
Disease	**Gene mutation**
Fanconi anemia	FANCA, FANCC
Dyskeratosis congenita	DKC1, TERC, TERT
Shwachman-Diamond syndrome	SBDS
10. Phenocopies of Inborn Errors of Immunity	
Disease	**Gene mutation**
anti-il-6 autoantibody disease	Acquired autoantibodies

Infections Associated with Inborn Errors of Immunity and Warning Signs in Affected Patients

Inborn errors of immunity (IEI) are genetically determined disorders of immune development or immune function that classically predispose to recurrent, severe, persistent, unusual, or opportunistic infections. Although infection remains the most recognised presentation, many patients also have autoimmunity, allergy, lymphoproliferation, enteropathy, inflammation, or malignancy, so infectious and noninfectious clues should be interpreted together[3,8]. Characteristic Infection Patterns in Major IEI Subsets in Adults are shown in Table I.

Types of infections associated with IEI

1. Recurrent sinopulmonary bacterial infections

These are among the commonest infectious presentations of IEI. Typical infections include recurrent otitis media, sinusitis, bronchitis, and pneumonia, especially those caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. This pattern is particularly characteristic of predominantly antibody deficiencies such as X-linked agammaglobulinaemia and common variable immunodeficiency, but it can also occur in combined immunodeficiencies[9].

2. Severe or recurrent skin and soft tissue infections

Patients with phagocyte defects and some combined immunodeficiencies may develop recurrent skin abscesses, cellulitis, furunculosis, osteomyelitis, or deep organ abscesses. *Staphylococcus aureus* is a common pathogen, and "cold" abscesses are a classic clue in autosomal dominant hyper-IgE syndrome[9].

3. Opportunistic fungal and protozoal infections

Opportunistic infections are a major warning clue for T-cell or combined immune defects. Important examples include *Pneumocystis jirovecii* pneumonia, mucocutaneous or invasive *Cryptosporidium parvum*, *Giardia lamblia*, and toxoplasmosis. *Candida* infection, *Aspergillosis*, *Cryptococcosis, Histoplasmosis*, and protozoal infections[9].

4. Viral infections that are severe, persistent, or extensive

Many IEI syndromes are associated with unusually severe or treatment-refractory viral disease. These include recurrent or disseminated herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus, molluscum contagiosum, and extensive human papillomavirus-related warts. Extensive cutaneous viral infections are especially characteristic of disorders such as DOCK8 deficiency and related combined immunodeficiencies[9].

5. Gastrointestinal infections and chronic diarrhea

Persistent or recurrent diarrhoea is a common infectious presentation in IEI, particularly in combined immunodeficiencies and immune dysregulation syndromes. Bacterial, viral, fungal, and protozoal causes are all reported, including *Salmonella*, *Campylobacter*, pathogenic *E. coli*, rotavirus, adenovirus, *Candida*, *Giardia*, and *Cryptosporidium*. In some patients, chronic enteric infection may lead to malabsorption, failure to thrive, or sclerosing cholangitis, especially with cryptosporidiosis[9].

6. Mycobacterial and vaccine-related infections

Disseminated bacillus Calmette-Guerin (BCG) infection, BCG adenitis, or disease due to nontuberculous mycobacteria are important clues to specific IEI pathways, particularly defects affecting IFN-gamma/IL-12 signaling or severe T-cell impairment. Severe adverse events after live vaccines, including disseminated BCG disease, vaccine-associated paralytic polio, or chronic rotavirus infection, should immediately

raise suspicion of an underlying IEI[9].

7. Central nervous system and invasive infections

Some patients present with meningitis, meningoencephalitis, septicaemia, liver abscess, or deep-seated invasive infection. Recurrent deep infection, sepsis, or infection at unusual sites is more informative than simple frequency of common viral URTI episodes[9].

need for prolonged therapy.

- Recurrent pneumonia, especially more than one severe episode or repeated lower respiratory infections.
- Failure to thrive, poor weight gain, or growth failure in children.
- Recurrent deep skin or organ abscesses.
- Persistent thrush or fungal infection of skin or mucosa after infancy.

Table I: Characteristic Infection Patterns in Major IEI Subsets in Adults

IEI Subset	Typical Pathogens/Infections	Clinical Clues
Autoinflammatory Disorders	Usually not characterised by recurrent infections; occasional secondary infections	Recurrent sterile inflammation and fever episodes
Combined Immunodeficiency (CID)	Recurrent bacterial, viral, fungal, and opportunistic infections; *Pneumocystis jirovecii*, CMV, EBV, *Candida* spp.	Severe or recurrent infections involving multiple organ systems
Predominantly Antibody Deficiencies (CVID, XLA, Selective IgA deficiency)	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*; recurrent sinusitis, otitis, pneumonia; recurrent sinusitis, otitis, pneumonia	Recurrent sinopulmonary infections, bronchiectasis
Immune Dysregulation Disorders	EBV, CMV, recurrent respiratory infections	Autoimmunity, lymphoproliferation, cytopenias accompanying infections
Congenital Phagocytic Defects (CGD, LAD)	*Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia*l *Aspergillus* spp., *Nocardia* spp.	Deep-seated abscesses, granulomas, poor wound healing
Defects in Intrinsic and Innate Immunity	Mycobacteria, HSV, VZV, HPV, invasive fungal infections	Severe infections with specific organisms despite otherwise normal immunity
Complement Deficiencies	*Neisseria meningitidis, Neisseria gonorrhoeae*	Recurrent meningococcal disease, septicaemia
Bone Marrow Failure Syndromes	Recurrent bacterial and fungal infections secondary to neutropenia	Cytopenias, marrow dysfunction
Phenocopies of IEI	Opportunistic infections resembling primary IEI	Autoantibodies or somatic mutations causing immune dysfunction
Combined Immunodeficiency with Syndromic Features (DiGeorge syndrome, AT, Hyper-IgE syndrome, WAS)	Recurrent bacterial, viral, and fungal infections depending on the underlying defect	Associated syndromic manifestations such as dysmorphism, eczema, ataxia, thrombocytopenia

Warning signs in patients with IEI

The traditional Jeffrey Modell warning signs remain useful as a screening framework, although recent evidence shows that they have higher specificity than sensitivity and may miss patients with predominantly noninfectious phenotypes. In practice, the most helpful warning signs are those that combine infectious severity with family history, treatment failure, or associated immune dysregulation.

Classical warning signs

- Multiple new ear infections within one year.
- Recurrent serious sinus infections within one year.
- Two or more months of antibiotics with little effect, or
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections, including septicaemia.
- Family history of IEI or early unexplained sibling deaths.

Additional warning signs beyond infection

Modern IEI recognition also requires attention to noninfectious clues. These include severe eczema, marked atopy, autoimmune cytopenias, lymphadenopathy, hepatosplenomegaly, granulomatous disease, chronic diarrhea, enteropathy, unexplained inflammation, and early-onset malignancy. Patients with these features may still have relatively few classic infections, so relying only on the old warning-sign lists can delay diagnosis[3].

The most suspicious pattern is not simply "frequent infection," because healthy children may also have repeated self-limited viral illnesses. More concerning features are severe infections, unusual organisms, opportunistic pathogens, poor response to standard antibiotics, repeated hospitalisations, infections at unusual sites, or infection combined with autoimmunity, eczema, lympho-proliferation, or growth failure. IEI should be considered at any age, since many antibody deficiencies and immune dysregulation syndromes present in adolescence or adulthood rather than infancy alone.

The infections associated with IEI span recurrent sinopulmonary bacterial disease, skin and deep abscess-forming infections, chronic gastrointestinal infection, severe viral disease, opportunistic fungal and protozoal infection, mycobacterial disease, and vaccine-related disseminated infection. Warning signs include recurrent severe infections, persistent thrush, deep abscesses, failure to thrive, need for intravenous antibiotics, and positive family history, but modern assessment must also include noninfectious red flags such as severe eczema, autoimmunity, enteropathy, and lymphoproliferation.

Approach to a patient with suspected IEI

A practical diagnostic approach begins with clinical suspicion. IEI should be considered in patients with recurrent, severe, unusual, or treatment-refractory infections; persistent thrush; skin or deep abscesses; failure to thrive; chronic diarrhoea; severe eczema or atopy; autoimmune cytopenias; unexplained lymphoproliferation; granulomatous inflammation; or a relevant family history. Suspicion should extend beyond children because many antibody deficiencies and immune dysregulation syndromes present in adolescence or adulthood[10].

A stepwise approach is useful:

1. Exclude secondary immunodeficiency caused by HIV or other infections, malnutrition, protein loss, malignancy, or immunosuppressive drugs.
2. Obtain baseline screening tests, including complete blood count with differential and peripheral smear, looking for lymphopenia, neutropenia, thrombocytopenia, abnormal leukocyte morphology, or syndromic haematologic clues.
3. Assess immune compartments with serum immunoglobulins (IgG, IgA, IgM), lymphocyte subset immunophenotyping by flow cytometry.
4. Use functional assays guided by phenotype, such as lymphocyte proliferation studies, neutrophil oxidative burst testing by DHR for chronic granulomatous disease, cytokine-response assays, and complement testing.
5. Proceed to molecular diagnosis using next-generation sequencing panels, whole-exome sequencing, or other genomic approaches, particularly in severe, syndromic, early-onset, familial, or diagnostically unresolved cases.
6. Refer early to a clinical immunologist because timely diagnosis changes outcomes, informs infection prophylaxis, immunoglobulin replacement, gene therapy options, and precision immunomodulation.

For severe combined immunodeficiency, urgency is critical because early diagnosis before major infection substantially improves outcome after haematopoietic stem cell transplantation. Newborn screening using T-cell receptor excision circles is an effective strategy for identifying many cases of SCID, though it does not detect all IEI. Diagnostic Approach to Suspected Inborn Errors of Immunity (IEI) in Adult shown in flowchart (Fig. 1).

Adult Patient with Suspected IEI

Clinical Assessment

- Recurrent, severe, unusual infections
- Autoimmunity
- Autoinflammation
- Lymphoproliferation
- Severe allergy/eczema
- Family history of IEI
- Early-onset malignancy

Initial Laboratory Evaluation

- CBC with differential count
- Peripheral smear
- Serum immunoglobulins (IgG, IgA, IgM, IgE)
- ESR/CRP
- HIV testing
- Basic biochemical profile (LFT. KFT, Total protein, A:G ratio, LDH, CRP)

Abnormal Findings?

Yes

Targeted Immunological Evaluation

- Lymphocyte subsets (CD3, CD4, CD8, CD19, CD16/56, CD7, CD57, CD45RA, CD45Ro, HLADR, CD25, CD24,CD38)

- Vaccine antibody responses
- Complement assays (CH50/AH50)
- Neutrophil oxidative burst (DHR)
- Functional immune assays

Phenotypic Classification

- Antibody deficiency
- Combined immunodeficiency
- Immune dysregulation
- Phagocytic defect
- Complement deficiency
- Innate immune defect

Genetic Evaluation

- Targeted gene panel
- Whole exome sequencing
- Whole genome sequencing

Definitive IEI Diagnosis

Management and Follow-up

- Immunoglobulin replacement
- Antimicrobial prophylaxis
- Targeted biologics
- Haematopoietic stem cell transplant
- Genetic counselling'

Fig. 1: *Diagnostic approach to suspected inborn errors of immunity (IEI) in adults.*

Although adult-onset severe combined immunodeficiency is uncommon, delayed diagnosis may lead to life-threatening opportunistic infections and hyperinflammatory complications. To highlight the diagnostic approach and pathological findings, we describe a representative case of disseminated cryptococcosis that revealed previously undiagnosed adult-onset SCID and was subsequently complicated by secondary haemophagocytic lymphohistiocytosis.

Case 1

A 42-year-old previously healthy male presented with a two-week history of persistent fever, generalised weakness, and progressive fatigue. He denied any history of recurrent infections, weight loss, chronic illness, immunosuppressive therapy, or prior hospitalisations. Physical examination revealed hepatosplenomegaly with bilateral sub-centimetric cervical lymphadenopathy. Initial laboratory investigations demonstrated pancytopenia with a haemoglobin level of 6.0 g/dL, total leukocyte count of 3.2 $\times$ 10 y/L, and a normocytic normochromic peripheral blood picture, while liver and renal function tests were within normal limits. In view of persistent fever and unexplained cytopenias, bone marrow aspiration and trephine biopsy were performed, revealing a hypocellular marrow with preserved trilineage haematopoiesis and numerous intracellular and extracellular fungal organisms, some exhibiting artefactual clearing. The fungal organisms stained positively with periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS), while strong mucicarmine positivity confirmed the diagnosis of disseminated cryptococcosis. Fine-needle aspiration cytology from a neglected scrotal swelling also demonstrated abundant cryptococcal organisms, further supporting disseminated fungal infection (Fig. 2).

As disseminated cryptococcosis in an HIV-negative individual raised suspicion for an underlying immunodeficiency, further investigations were undertaken. Serological tests for HIV, hepatitis B and C, and autoimmune markers were negative, whereas serum immunoglobulin levels were markedly reduced. Flow cytometric immunophenotyping demonstrated profound lymphopenia with markedly reduced T-cells (342 cells/mm^3), B-cells (53 cells/mm^3), and NK cells (12 cells/mm^3), consistent with

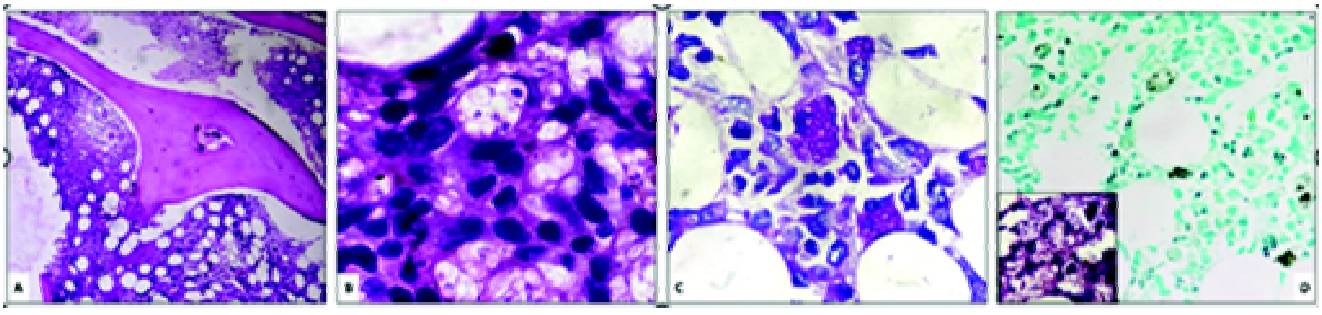


Fig. 2: *(A and B) Ante-mortem bone marrow biopsy demonstrating marrow involvement by Cryptococcus infection (100 x and 400 x, H and E). (C) Periodic acid–Schiff (PAS) stain highlighting fungal organisms (400 x) (D) Gomori methenamine silver (GMS) stain (200 x) demonstrating the fungal spores, with mucicarmine stain shown in the inset.*

severe combined immunodeficiency (SCID) or a late-onset combined immunodeficiency phenotype. The patient was treated with intravenous amphotericin B followed by high-dose fluconazole and broad-spectrum antibiotics; however, despite aggressive therapy, he developed progressive multiorgan dysfunction and succumbed to cardiac arrest. Post-mortem bone marrow examination revealed extensive hemophagocytosis with numerous CD68-positive histiocytes containing fungal organisms and engulfed haematopoietic cells. Retrospective review of laboratory investigations showed marked hyperferritinaemia (3,600 ng/mL) and hypertriglyceridaemia, fulfilling the diagnostic criteria for secondary haemophagocytic lymphohistiocytosis (HLH). This case illustrates a rare presentation of occult adult-onset SCID unmasked by disseminated cryptococcosis and complicated by fatal infection-associated HLH.

The following case highlight the diverse clinical spectrum of adult-onset inborn errors of immunity (IEI) presenting with visceral leishmaniasis. Owing to impaired cell-mediated immunity, patients with IEI are predisposed to severe, recurrent, or atypical infections, which may be the first manifestation of an underlying immune defect in adulthood.

Case 2

A 27-year-old previously undiagnosed male presented with fever, marked haepatosplenomegaly (liver 15.8 cm, spleen 19 cm), and bicytopenia with macrocytic anaemia (Hb 8 g/dL; MCV 100 fL) and leukopenia. Laboratory evaluation showed low ferritin (87.6 ng/mL) with normal platelet count on manual estimation. Bone marrow examination revealed a hypocellular marrow (approximately 50 - 60% cellularity for age) with trilineage haematopoiesis, prominent megaloblastic erythroid hyperplasia with dyserythropoietic changes, adequate megakaryopoiesis, increased histiocytes exhibiting haemophagocytosis, and no evidence of atypical cells, granulomas, or hematological malignancy. Bone marrow aspirate and imprint smears demonstrated both intracellular and extracellular amastigote forms of *Leishmania donovani*, confirming visceral leishmaniasis (Figure 3). The patient was advised vitamin B12/folate assessment along with specific evaluation and treatment for leishmaniasis. In view of the occurrence of disseminated visceral leishmaniasis in a young adult without an apparent secondary cause, an underlying inborn error of immunity (IEI) was considered. This case underscores that adult-onset IEI should be included in the differential diagnosis of visceral leishmaniasis presenting with cytopenias and haepatosplenomegaly, particularly after exclusion of haematological malignancy, as recognition of an underlying primary immunodeficiency has important implications for targeted immunological evaluation, genetic testing, management, and long-term follow-up.

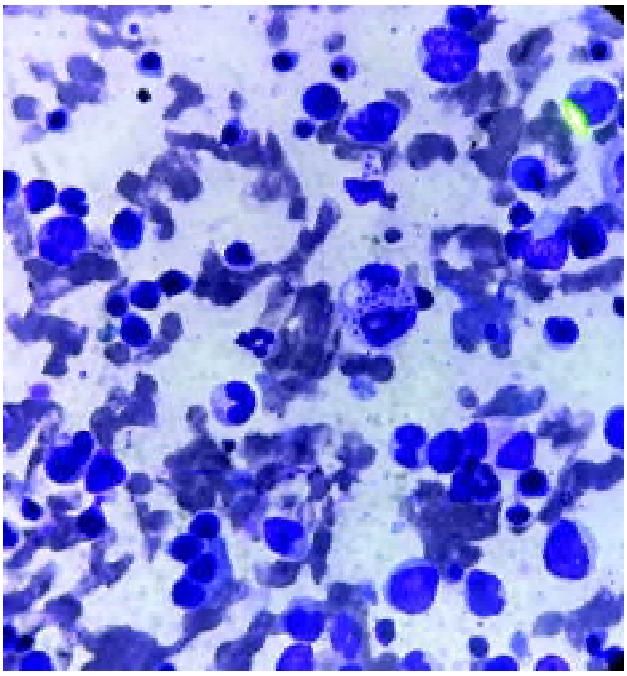


Fig. 3: *Bone marrow aspirate smears demonstrating amastigote forms of Leishmania donovani.*

Discussion

The modern IEI framework is no longer limited to recurrent infection syndromes. Instead, it encompasses disorders of host defence, immune regulation, inflammation, allergy, and predisposition to malignancy, linked by molecular defects in immune pathways. This broader view is especially relevant in adult medicine and pathology-based practice, where autoimmune, granulomatous, lymphoproliferative, or inflammatory presentations may precede recognition of an underlying IEI.

In the Indian context, under-recognition remains a major challenge. Expansion of national registries, improved access to flow cytometry and genomic testing, and greater clinician awareness are essential for defining the true epidemiology and improving patient outcomes.

The diagnostic evaluation of IEI is challenging because these disorders are clinically heterogeneous and may present at any age with infectious or non-infectious manifestations.

Although recurrent infections remain a major clue, many patients first come to attention because of autoimmunity,

severe eczema, enteropathy, lymphoproliferation, unexplained inflammation, or malignancy risk, which can delay recognition if clinicians rely too narrowly on classic warning signs. A major strength of the modern approach is the use of phenotype-directed testing. Careful characterisation of the infection pattern, age at onset, family history, vaccine reactions and associated immune dysregulations helps direct the initial laboratory panel and avoid indiscriminate testing. In this setting, basic investigations such as CBC, immunoglobulin levels, lymphocyte subsets, complement assays, and neutrophil oxidative burst testing remain highly valuable because they rapidly identify broad immune-compartment defects and help prioritize more specialised studies.

At the same time, laboratory diagnosis has clear limitations. Normal screening tests do not exclude IEI, especially in patients with subtle immune dysregulation, pathway-specific defects, or phenocopies, and the quality and standardisation of non-functional immunological assays can vary across laboratories. For this reason, functional assays and genomic testing have become increasingly important, particularly when the phenotype is severe, syndromic, early in onset, familial, or unexplained after first-line evaluation.

Genetic testing has transformed the field by moving diagnosis from broad clinical syndromes towards molecularly defined disease.

Overall, the most effective strategy is a tiered and multidisciplinary one that integrates clinical suspicion, screening immunology, targeted functional studies, and genetic confirmation. Such an approach improves diagnostic yield, reduces delay, and supports timely initiation of immunoglobulin replacement, antimicrobial prophylaxis, haematopoietic stem cell transplantation, or other targeted therapies.

Conclusion

Inborn errors of immunity are a rapidly expanding group of genetically determined disorders with diverse infectious and non-infectious manifestations. Current IUIS classifications recognize hundreds of genes and phenotypes, and clinical evaluation increasingly depends on integrating phenotype, immunologic testing, and genomic analysis. Western data suggest that IEI is more common than historically believed, while Indian prevalence remains incompletely defined because of underdiagnosis and limited registry capture. A structured, stepwise diagnostic approach is essential for early recognition, subtype definition, and institution of targeted therapy.

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