

Combined T and B Cell Immunodeficiencies

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Introduction

The immune system is divided into humoral and cellular mechanisms. B cells are known for their role in humoral immunity by secreting antibodies against various pathogens, and T cells are responsible for cell-mediated immunity by killing intracellular organisms. T cells are also necessary in the maturation of B cells into antibody-secreting plasma cells.

In 1958, Hitzig et al. reported the first case of combined deficiency of cellular and humoral immunity systems in a patient affected by agammaglobulinemia, mucocutaneous candidiasis, intractable diarrhea, and interstitial pneumonia [1]. Combined immunodeficiencies (CIDs) consist of a heterogeneous group of PIDs characterized by impairment in the development and/or function of T cells. In addition, various defects of NK cells were also observed in this group of disorders. Even with normal maturation of B cells, their function is defective due to the regulatory role of T helper cells in humoral immunity.

It is estimated that one out of five patients with PIDs has CID [2]. Since the immune system in these disorders is unable to maintain an efficient defense, recurrent infections are common, resulting in serious morbidity and mortality. Impairment in the regulatory function of T cells increases the susceptibility of affected subjects to autoimmune reactions. To make matters worse, malignancies are more prevalent in CID patients due to the lack of cellular immunity which is critical in the immune response against tumor cells [3].

If a patient is affected by severe combined immunodeficiency (SCID), its typical clinical manifestations generally present in the first year of life. However, in some rare types of CID, evidence of immunodeficiency may be initially absent, while other clinical features are present. For more details, see Chap. 2 of the book *“Primary Immunodeficiency Diseases: Definition, Diagnosis and Management*, edited by Rezaei N, Aghamohammadi A, Notarangelo LD; Springer.”

Case 2.1 with Diffuse Rash After Vaccination

Presented by Francisco A. Bonilla

An 18-month-old boy presents for evaluation of a diffuse rash. Three weeks ago he received the varicella vaccine. Over the last 2 or 3 days, he has had the rapid progression of a diffuse rash with the classic appearance of chicken pox. He was born at term and was healthy for the first year of life. In the last 6 months, he has had many episodes of upper respiratory infections, otitis media, and bronchopneumonia. He has had little time off antibiotics. He has no other medical problems. There is no family history of immunodeficiency; his parents are first cousins. On examination, he is afebrile, tachycardic, and tachypneic. He has hundreds of pox lesions over his entire body; he is grunting with respiration. The CXR shows bibasilar infiltrates. He is admitted for aggressive management of presumed disseminated varicella. A polymerase chain reaction (PCR) on vesicle fluid reveals vaccine strain varicella.

Q1. How should the evaluation proceed?

- A. Rare children with healthy immune system can develop disseminated vaccine strain varicella, and immune evaluation is not required.
- B. This could be SCID and since bone marrow transplantation (BMT) should be performed urgently, rapid diagnosis is essential. Specialized tests for all common forms of SCID should be sent immediately.
- C. The child may be immune deficient, but he is too ill for testing to be informative. Any immune evaluation should be deferred until a few weeks after he recovers.
- D. Screening tests of humoral and cellular immune function should be sent and interpreted first; specialized testing should wait for guidance from these results.

Answer: *The correct answer is D.*

Any individual who develops disseminated life-threatening disease due to attenuated vaccine-strain organisms is immunodeficient, by definition. It is extremely wasteful to send many complex and expensive tests without initial evaluation of basic immune parameters. One might get “lucky” and hit upon the right diagnosis, but it is unlikely that one would “save” time in this way. It is possible that immunologic testing may be affected by severe infection, but this should not delay evaluation. One cannot predict the future course and must simply interpret tests in light of the current clinical situation [4].

Immunologic evaluation shows an IgG normal at 820 mg/dL, IgA normal at 102 mg/dL, and IgM mildly elevated at 233 mg/dL. *Haemophilus influenzae* antibody was not detected; tetanus antibody was protective at 0.6 IU/mL (>0.5). The total lymphocyte count is 180 cells/mm³. Of these, 7 % are T cells, 40 % NK cells, and 45 % B cells. There is no response at all to mitogens in vitro.

Q2. Which statement is true?

- A. All of the laboratory immunologic abnormalities could be secondary to the severe viral illness.
- B. This testing is consistent with X-linked hyper IgM (CD40 ligand deficiency).
- C. This cannot be SCID because the IgG is normal.
- D. This cannot be SCID because he has survived to 18 months of age.

Answer: *The correct answer is A.*

At presentation, it is not clear which immunologic abnormalities may be due to the severe viral illness but SCID cannot be ruled out at that point. Some lymphopenia due to bone marrow suppression is possible. In such a circumstance, one would more often see diminished mitogen responses rather than complete lack of response [5]. This consideration should not discourage or cause delay in consideration of the diagnosis of an immunodeficiency, but would require one to keep an open mind in pursuit of the specific diagnosis. This evaluation is not consistent with CD40 ligand deficiency/X-linked hyper IgM (HIGM) syndrome. In patients with XHIGM, IgG

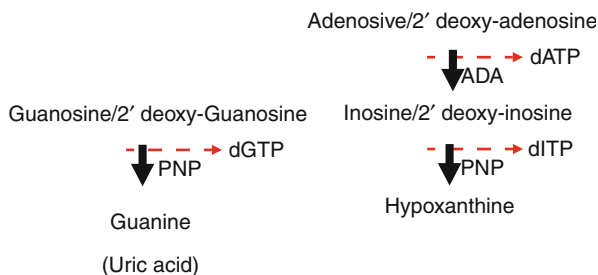


Fig. 2.1 Reactions catalyzed by ADA and PNP in degradation of purine nucleotides. Lack of ADA leads to accumulation of dATP. Lack of PNP leads to accumulation of dGTP and dITP. All of these are toxic to lymphocytes and neurons. The block in degradation of guanosine by PNP (that does not occur in ADA deficiency) leads to low levels of uric acid in blood and urine

and IgA are generally very low or absent, and mitogen responses are most often normal [4, 6]. Although most SCID is associated with hypo- or agammaglobulinemia, presentation is variable, and it is not possible to exclude all forms of SCID on that basis alone [5]. Similarly, while many untreated children with SCID die in the first year of life, some milder forms or progressive forms may not develop life-threatening infections until later.

- Q3. If this is a SCID, which of the following is most likely to yield a definitive diagnosis?
- A. Flow cytometry to determine γ c expression (X-linked SCID)
 - B. Sequence analysis of the interleukin-7 receptor α chain gene (*IL7RA*)
 - C. Measurement of red blood cell ADA and PNP levels
 - D. Western blot for JAK3

Answer: The correct answer is C.

Once again, even though some B and NK cells are present, the numbers are far below the normal range for age, and this could be alymphocytic SCID [4, 7, 8]. The most appropriate test to begin with in this setting is measurement of ADA and PNP activities. This patient had undetectable nucleoside phosphorylase activity in his red blood cells and has PNP deficiency [9]. Interestingly, this patient also had undetectable serum uric acid (see Fig. 2.1). Although this finding is suggestive, it is not sufficient for definitive diagnosis.

- Q4. Which statement is correct?
- A. The patient has normal IgG and normal tetanus antibody, and BMT is unnecessary.
 - B. Immune function should be followed over time; BMT should be considered if there is further deterioration or other severe infections.
 - C. Preparation for BMT should proceed without delay.
 - D. BMT is not curative of PNP deficiency.

Answer: The correct answer is **C**.

It is well known that the immune deficiency of PNP is progressive [10, 11]. Lymphocytes slowly accumulate toxic levels of dGTP and dITP over time (Fig. 2.1). This is the reason for the late presentation in this disorder. This child still has some plasma cells secreting immunoglobulins, but these are likely to disappear with time and will not be replaced. Since there will only be further deterioration with time, it makes no sense to wait to perform BMT. Fortunately, this is curative for many patients.

Practical Points

- The family history is critically important for the early detection of immunodeficiency, especially SCID.
- Severely impaired (usually absent) T cell response to mitogens in vitro is an essential element of the diagnosis of SCID.
- Not only percentages but also absolute numbers should be kept in mind when phenotypically classifying SCID.

Case 2.2 with Chronic Cough

Presented by Francisco A. Bonilla

A 7-week-old male infant presents to a pulmonology clinic with a 5-week history of cough. This is his third evaluation for this illness. He has been afebrile, has had no symptoms other than cough, and has been feeding well, but gaining weight slowly. The cough is getting progressively worse. The child had been born vaginally at term and had an uncomplicated nursery stay. He had a few days of heme-positive stools that resolved spontaneously. He has had two prior chest X-rays (CXR) at another institution that have been read as normal (the most recent was 1 week ago). He also had a normal electrocardiogram (EKG). The family history is unrevealing; there is no consanguinity. On examination, he is alert and afebrile with normal vital signs. He is coughing frequently and grunting with respiration. Lung auscultation reveals diffuse rales and diminished sounds on the right side. Another CXR is obtained and shows diffuse interstitial markings and a dense right middle lobe infiltration. He is admitted to the hospital for further evaluation and treatment. His WBC is 4,400/mm³ (58 % neutrophils, 2 % lymphocytes, 21 % monocytes, and 10 % eosinophils). Cultures obtained at bronchoscopy grew *Stenotrophomonas maltophilia*.

- Q1. If this child has an immunodeficiency, which is the most likely diagnosis?
- A. A form of agammaglobulinemia
 - B. A form of HIGM
 - C. Complete DGS
 - D. A form of SCID

Answer: *The correct answer is D.*

The total lymphocyte count is 88 cells/mm³. This is profound lymphopenia, especially in a child at this age [7, 8]. The median count is >5,000 cells/mm³ and the 10th percentile is approximately 3,400. This degree of lymphopenia is not at all characteristic of any of the agammaglobulinemias or HIGM [4]. Complete agenesis of the thymus (complete DGS) can be associated with lymphopenia, although it is not usually so profound, due to the presence of a small number of T cells and normal numbers of B cells. Furthermore, the absence of a cardiac defect and hypocalcaemia make DGS less likely, although not impossible. The best choice is D, given the overall presentation and the profound lymphopenia. Note that severe lymphopenia is one of the most consistent and important early signs of SCID [12]. The degree of lymphopenia in this patient was not appreciated right away. The result of the BAL culture led to evaluation for CF by sweat chloride measurement and genetic testing which were normal.

- Q2. Which of the following would support a diagnosis of SCID?
- A. Evidence of thymic hypoplasia
 - B. Absent response to mitogens in vitro
 - C. Absent serum IgG
 - D. Absence of 22q11 deletion

Answer: *The correct answers are A and B.*

Review of this patient's CXR revealed that the thymus shadow was absent on all. An ultrasound confirmed the atrophic, rudimentary nature of the thymus. Although a small thymus is characteristic of most forms of SCID [4], a small or even normal-appearing thymus may be seen in some, including deficiencies of the CD3 delta chain and ZAP-70 [13], coronin 1A [14], or hypomorphic mutations of the cytokine receptor common gamma chain (γ c) [15]. Furthermore, complete DGS would also be associated with absence of a thymic shadow on CXR [16]. Although the severe lymphopenia may make interpretation of the test difficult, it is essential to demonstrate the absence of detectable T cell function on the path toward diagnosis of SCID [4]. IgG may actually be normal early in the course of disease, since this comes from transplacental transfer from the mother in utero. Only approximately half of infants with complete DGS will have 22q11 deletion, so this diagnosis cannot be excluded on this basis [16]. This patient was tested for 22q11 deletion, which was not found.

- Q3. If this is SCID, which of the following tests is most likely to yield a definitive diagnosis in this case?
- A. Western blot for JAK3
 - B. Flow cytometry to determine X-linked SCID
 - C. Sequence analysis of the *IL7RA* gene
 - D. Measurement of red blood cell ADA and PNP

Answer: *The correct answer is D.*

Table 2.1 Gene defects associated with various SCID lymphocyte phenotypes^a

All are T ⁺	B ⁺	B ⁻
NK ⁺	T ⁺ B ⁺ NK ⁺ : <i>IL7RA</i> (IL-7 receptor α) <i>CD45</i> <i>CD3D</i> (CD3 delta) <i>CD3E</i> (CD3 epsilon) <i>CD247</i> (CD3 zeta) <i>CORO1A</i> (coronin 1A) <i>WHN</i> (winged helix nude)	T ⁺ B ⁺ NK ⁺ : <i>RAG1</i> (recombinase-activating gene 1) <i>RAG2</i> (recombinase-activating gene 2) <i>DCLRE1C</i> (Artemis) <i>LIG4</i> (DNA ligase IV) <i>NHEJ1</i> (Cernunnos) <i>PRKDC</i> (DNA-dependent protein kinase)
NK ⁻	T ⁺ B ⁺ NK ⁻ : <i>IL2RG</i> (gamma-c) <i>JAK3</i> (Janus kinase 3)	T ⁺ B ⁺ NK ⁻ (alymphocytosis): <i>ADA</i> (adenosine deaminase) <i>NP</i> (nucleoside phosphorylase) ^b <i>AK2</i> (adenylate kinase 2) ^c
Variant phenotypes	<i>CD8</i> , <i>ZAP70</i> , MHC class I (<i>TAP1</i> , <i>TAP2</i>): low CD8 cells, normal CD4 cells MHC class II (<i>CIITA</i> , <i>RFX5</i> , <i>RFXAP</i> , <i>RFXANK</i>): low CD4, normal CD8 <i>STIM1</i> , <i>IL2RA</i> , <i>STAT5B</i> , <i>ITK</i> , <i>DOCK8</i> : low or normal total T cells	

^aThese are the most characteristic phenotypes associated with these gene defects. The phenotype may be variable depending on the specific mutation (e.g., hypomorphic), maternal engraftment of T cells, or oligoclonal expansion of autoreactive T cells (Omenn syndrome)
^bThe phenotype of *NP* mutations is highly variable, and there is a tendency toward progressive decrease in lymphocyte counts over time
^c*AK2* is a mitochondrial gene

Mitogen proliferation was completely absent in this patient, indicating SCID. Given the profound lymphopenia, flow cytometry will probably not be helpful in determining which forms of SCID should be specifically sought. Functional T cells are absent in all cases of SCID [4]. Depending on the particular molecular defect, B and NK cells may or may not be present. Thus, SCID is generally classified into four different groups (Table 2.1) [17]. X-linked SCID (γ c deficiency), *IL7RA* mutation, and *JAK3* deficiency are all associated with normal, or near normal, numbers of B cells [4]. Therefore, none of these are likely to be the underlying cause of SCID in this patient. *ADA* deficiency is the most common cause of SCID with autosomal recessive inheritance, and in its severe form, characteristically presents with alymphocytosis [18]. The lack of *ADA* leads to the accumulation of high levels of dATP which is toxic to lymphocytes (Fig. 2.1). This patient was found to have an undetectable level of *ADA* activity.

- Q4. What modalities are available to treat this disease?
- A. Enzyme replacement therapy
 - B. Bone marrow transplantation
 - C. Gene therapy
 - D. All of the above

Answer: *The correct answer is D.*

A polyethylene glycol-conjugated form of bovine adenosine deaminase (pegademase bovine, or Adagen) is available for therapy for ADA deficiency if BMT is not favorable (lack of a suitable donor, family preference). Immune reconstitution is generally not complete, but may be adequate along with IgG replacement therapy for sufficient protection to afford a reasonably normal lifestyle [19]. Unfortunately, the benefit of this treatment often wanes to some degree over time (5–10 years) due to the production of antibodies to the drug. BMT may offer a complete cure of the immunodeficiency of ADA deficiency [20]. Our patient was fortunate to have an HLA-identical sister who donated marrow which was infused without manipulation or prior conditioning. He now has normal T, B, and NK cell numbers, normal T cell function, and normal immunoglobulin levels. Recently, gene therapy has also become available for a small number of ADA-deficient patients enrolled in clinical trials [21]. These patients do not have suitable bone marrow donors. Immune reconstitution was adequate in most, and of the 30 patients treated, none have yet died after a median of 4 years (range 1.8–8 years) of follow-up. Unfortunately, there is no available therapy for the neurological sequelae of ADA deficiency [22]. As many as half of patients surviving with good immune reconstitution will have one or more of the following: cognitive impairment, motor neuropathy, and sensorineural hearing deficit. Unfortunately, our patient is now 8 years old and does not speak, has hearing loss, and has poor gross motor skills.

Practical Points

- Several factors may confound the “classic” lymphocyte phenotype of a particular form of SCID; these include maternal T cell engraftment, the specific genetic mutation (hypomorphic), or oligoclonal T cell expansion (Omenn syndrome).

Case 2.3 with Oral Thrush and Pneumonia

Presented by Francisco A. Bonilla

A 5-month-old baby is referred for outpatient evaluation for recurrent infections. He was born at term via caesarean section for fetal distress. He was well until 2 months of age when he began to have oral thrush. These lesions responded well to nystatin but recurred quickly when the medication was stopped. He also had three respiratory infections for which he was hospitalized; at least one was pneumonia with a positive CXR. The family history is notable for the parents being first cousins. In addition, the patient’s mother had five brothers (by two different fathers), four of whom died in infancy due to infections. The fifth received bone marrow transplantation (BMT) for PID and subsequently died. On examination, the patient is a normally developed male infant in some apparent discomfort. His weight is 6.9 kg

(25th percentile); his length is 66 cm (75th percentile). Both ear canals were filled with pus. Chest auscultation was notable for mild diffused rhonchi. He had a balanitis with swelling around the glans of penis with some purulent drainage.

Q1. Which is the most likely diagnosis?

- A. X-linked SCID
- B. X-linked HIGM
- C. X-linked agammaglobulinemia
- D. There is insufficient information to distinguish between these diagnoses.

Answer: *The correct answer is D.*

The family history contains an element that is suggestive for increased risk of an autosomal recessive defect (parental consanguinity). However, the maternal history of five affected male siblings with two different fathers is highly suggestive of an X-linked nature of the disease, with the maternal grandmother being a carrier. If our patient is affected, then his mother must also be a carrier. This clinical presentation is consistent with any of the three diagnoses listed [4]. X-SCID (cytokine receptor common gamma chain deficiency) is the most common form of SCID accounting for half of all cases, and this presentation is entirely consistent [23]. X-linked HIGM (XHIM, CD40 ligand deficiency) may also present in infancy with these types of infections [6]. X-linked agammaglobulinemia (XLA or Bruton's tyrosine kinase deficiency) usually presents somewhat later in infancy, and oral thrush is not characteristic, but it could certainly be present in a patient with XLA [24]. The other infectious problems in this infant are certainly consistent with XLA.

Immunologic evaluation shows IgG 96 mg/dL, IgM 6 mg/dL, and IgA not detected. The total lymphocyte count is $2,695/\text{mm}^3$. The percentage of CD4^+ T cells is 8 % (absolute count $216/\text{mm}^3$), CD8^+ T cells is 45 % (absolute count $1,213/\text{mm}^3$), B cells is 43 % (absolute count $1,159/\text{mm}^3$), and NK cells is 2 % (absolute count $54/\text{mm}^3$). Lymphocytes have no response to mitogens in vitro.

Q2. Which of the following statements is correct?

- A. This cannot be SCID; there are too many T cells.
- B. The most likely diagnosis is X-linked SCID.
- C. The most likely diagnosis is a defect associated with MHC class II expression.
- D. The most likely diagnosis is JAK3 deficiency.

Answer: *The correct answer is B.*

The absence of mitogen response is essentially diagnostic of SCID [4]. Although there are some T cells and B cells present (these levels of CD8^+ T cells and B cells are actually normal for an infant at this age), this level of lymphocytes still represents a striking lymphopenia for this age due to the near absence of CD4^+ cells and NK cells [7, 8]. The lymphocyte phenotype is at least suggestive of the possibility of the diagnosis of MHC class II deficiency (Table 2.1), and there is parental consanguinity as well. However, the low NK cell number is not consistent with this.

Furthermore, the family history is overwhelmingly suggestive of an X-linked pattern of inheritance, and the genetic defects associated with lack of MHC class II expression are very rare (less than 50 cases reported worldwide), while X-linked SCID accounts for half of all cases of SCID [4]. The lymphocyte phenotype characteristically associated with specific genetic defects may be affected by a variety of factors, including engraftment of maternal T cells that cross the placenta in utero or enter the fetal circulation at birth. In this patient, the normal level of CD8⁺ cells is the result of maternal engraftment, which was demonstrated by fluorescence in situ hybridization showing a proportion of Y-chromosome-negative lymphocytes equivalent to the CD8⁺ cells. This patient has T⁻B⁺NK⁻ SCID. X-SCID and JAK3 deficiency could both be considered; however, as already mentioned, the history favors X-linked disease. This patient was found by genetic analysis to have a mutation in the gene (*IL2RG*) encoding the cytokine receptor gamma chain (X-SCID).

Q3. Which of these therapies should be instituted?

- A. Antibiotics
- B. IgG replacement
- C. PCP prophylaxis
- D. All of the above

Answer: The correct answer is **D**.

The patient has evidence of active infection. Antibiotics should have been initiated even before immunologic evaluation was undertaken. There is agammaglobulinemia, so IgG replacement is essential [25]. This therapy is critical for infection prophylaxis in anticipation of BMT or other definitive therapy. In the absence of T cell function, the patient is also at risk of opportunistic infections such as *Pneumocystis* pneumonia.

Q4. When should BMT be performed?

- A. BMT should only be performed if a fully matched donor can be found.
- B. BMT should be performed as soon as possible.
- C. BMT should be performed after 1 year of age to reduce the long-term sequelae of myeloablative therapy.
- D. BMT should not be performed unless it is justified by the occurrence of opportunistic infections.

Answer: The correct answer is **B**.

BMT should be performed as soon as possible, using the best donor available. However, there is no need to wait for a specific type of donor. BMT performed within the first month of life has the best outcome [25]. BMT within the first 3.5 months of life has significantly better outcome than BMT performed later [26]. Unfortunately, our patient has already missed both of these windows of opportunity. Even more unfortunately, this was unnecessary. Given this child's family history, any male children of this mother should have had immunological testing at birth [4]. There is some debate as to which type of donor and technique of transplantation

is associated with the best outcomes. However, if the only donor available is a haploidentical parent, then BMT should proceed as quickly as possible anyway since outcomes often are quite good, regardless of whether myeloablation is performed or not [26]. Radiation is sometimes used for myeloablation, except in the youngest children, due to neurotoxicity. However, this modality is not absolutely necessary in any case. Note that gene therapy is another mode of therapy that is available to treat X-SCID [27]. About 20 patients have been treated thus far with various protocols. Most have had complete immune reconstitution. Several have developed leukemia due to mutagenic gene insertion events. Newer gene therapy vectors have been engineered to minimize this possibility.

Practical Points

- IgG replacement and antimicrobial prophylaxis should be initiated in all infants with SCID in advance of BMT.
- BMT or gene therapy should be pursued as rapidly as possible in order to achieve the best outcomes.

Case 2.4 with Pneumonia, Failure to Thrive, and Oral Candidiasis

Presented by Waleed Al-Herz

A 3-week-old male, who was born to related parents, is being evaluated for interstitial pneumonia, failure to thrive (FTT), and oral candidiasis. Physical examination shows a sick-looking, underweight patient with flaring of the costochondral junctions.

Laboratory data reveals WBC 3,500/mm³ (neutrophils 85 %, lymphocytes 5 %, monocytes 5 %, eosinophils 3 %, and basophils 2 %), IgG 384 mg/dL, IgM <4 mg/dL, and IgA <6 mg/dL. Lymphocyte subset analysis shows CD3⁺ T cells 4 %, CD4⁺ T cells 2 %, CD8⁺ T cells 0.8 %, CD19⁺ B cells 7.5 %, and CD16⁺,CD56⁺ NK cells 50 %.

- Q1. Which of the following can be a possible diagnosis?
- A. X-SCID
 - B. Reticular dysgenesis
 - C. Immunodeficiency due to defects of purine metabolism
 - D. JAK3 deficiency

Answer: *The correct answer is C.*

Immunodeficiency due to defects of the purine metabolism (ADA and PNP) was found to cause approximately 20 % of all cases of SCID [28]. Because of the toxic metabolites, the disease is characterized by attrition of the immune system and has

a wide range of clinical manifestations [29]. X-SCID is characterized by normal or increased B cell counts, while patients with ZAP-70 have isolated CD8⁺ lymphopenia [30, 31]. In contrast, reticular dysgenesis, which is caused due to defect in adenylylate kinase 2, is characterized by defective maturation of both T and B lymphocytes associated with granulocytopenia and deafness [32].

Q2. Which of the following is true about ADA deficiency SCID?

- A. Fifty percent of the patients have abnormality of costochondral junctions.
- B. Some patients may have delayed onset of the disease and present with autoimmunity.
- C. A group of ADA-deficient subjects may have normal clinical phenotype.
- D. All of the above.

Answer: *The correct answer is D.*

Among the non-immunologic manifestation of ADA deficiency SCID is that approximately 50 % of the patients have abnormality of costochondral junctions best seen on lateral CXR [33]. An increasing number of patients are being described with diagnosis made beyond infancy and even in adulthood. This appears to be due to the retention of some ADA activity [34]. An additional group of individuals may have absence of ADA activity in erythrocytes with normal clinical phenotype due to significant ADA activity in non-erythroid cells [35].

Q3. Which of the following is true about ADA deficiency SCID?

- A. The diagnosis can be made using an enzyme assay.
- B. Cases with reverting mutations may show improvement overtime without interventions.
- C. Sensorial and cognitive abnormalities can frequently affect patients.
- D. All of the above.

Answer: *The correct answer is D.*

The diagnosis of ADA deficiency can be made by enzyme assay of erythrocytes and lymphocytes or DNA analysis for previously reported deleterious mutations. Somatic mosaicism due to reversion to normal of inherited mutations in *ADA* gene can result into improvement of clinical phenotype despite absence of any interventions [36]. It has been well documented that ADA-deficient SCID patients are frequently affected by cognitive and behavioral abnormalities which appear to be unique to this form of SCID [37, 38].

Q4. All of the following therapeutic interventions should be considered in ADA-deficient SCID patients except:

- A. Haploidentical HSCT
- B. Enzyme replacement therapy in the form of polyethylene glycol (PEG-ADA)
- C. Gene therapy
- D. Intravenous immunoglobulins (IVIG)

Answer. The correct answer is A.

Allogeneic HSCT from a histocompatible donor is the therapy of choice for ADA-deficient SCID at this point. It appears that these patients are not candidates for haploidentical transplantation from a related donor due to poor outcome [39]. Enzyme replacement therapy in the form of PEG-ADA was found to be effective in improvement of the clinical phenotype with less opportunistic infections and restoration of normal growth and development. However, there was partial immune reconstitution with this form of therapy, and a significant number of patients were found to develop antibody against the bovine ADA protein [40–42]. It has been proven that gene therapy by means of introduction of ADA complementary DNA (cDNA) into stem cells is an acceptable therapy for patients with no HLA-matched donors [21].

Practical Points

- The absence of tonsils and hypoplasia of lymphoid tissue and thymus are frequent features of the disease.
- SCID patients are usually classified according to the distribution of lymphocyte subsets (T, B, and NK cells)."
- All patients with unexplained lymphopenia, regardless of the age, should be evaluated for ADA deficiency.
- Non-immunologic manifestations are frequent in ADA-deficient patients.
- Patients suspected to have ADA deficiency and had history of blood transfusion should have DNA analysis for previously reported deleterious mutations in case they show normal ADA activity.
- Neutralizing antibodies may impair the function of PEG-ADA, and patients may require an increase in the dosage or discontinuation of treatment.
- Prompt evaluation and referral for HSCT is lifesaving.

Case 2.5 with *Candida* spp. Infections and *Pneumocystis jirovecii* Pneumonia

Presented by Teresa Espanol

A 7-month-old girl is being evaluated for suspected immunodeficiency. She has a history of recurrent gastrointestinal infections and mucocutaneous candidiasis since 2 weeks of age with poor response to specific therapy. She had *Pneumocystis jirovecii* pneumonia at 3 months of age and respiratory tract infection requiring admission and intravenous antibiotic therapy (a positive blood culture for *Streptococcus pneumoniae*). Her weight is below the 5th percentile. The parents are

non-consanguineous and there is no family history of immunodeficiency. The pregnancy was uneventful. Laboratory findings include WBC 10,070/mm³ (neutrophils 36 %, lymphocytes 63 %); normal immunoglobulin levels, including IgE; and normal liver and kidney function tests. Lymphocyte subset analysis by flow cytometry includes CD3⁺ 71 %, CD4⁺ 41 %, CD8⁺ 30 %, CD19⁺ 25 %, and NK cells 3 %. Phytohaemagglutinin (PHA)-stimulated lymphocyte proliferation is normal.

- Q1. What is the most likely diagnosis?
- A. Severe combined immunodeficiency (SCID)
 - B. Combined immunodeficiency (CID)
 - C. Hyper IgE syndrome (HIES)
 - D. DiGeorge syndrome (DGS)

Answer: *The correct answer is B.*

Combined immunodeficiency (CID) is a wide group of PIDs that are being progressively defined with molecular studies. They are characterized by repeated bacterial and opportunistic infections, usually less severe than in classical SCID patients. Lymphocyte subsets and T cell proliferation could be near normal. At this point prophylactic antibiotics and antifungal drugs are used [43, 44].

- Q2. For the above mentioned case, which of the following approaches could make a most probable diagnosis?
- A. Obtaining the family history
 - B. Lymphocyte subsets analysis
 - C. T cell function analysis
 - D. Molecular studies of IL-2 receptor on T lymphocytes

Answer: *The correct answers are B and C.*

The differential diagnosis of CID from SCID is crucial. Therapy in the latter case is always hematopoietic stem cell transplant (HSCT). In most cases of CID, there is no molecular defect already available, probably due to the heterogeneity of the cases described and lack of family history; and thus, therapy of the current infections and prophylactic antibiotics are used [43].

The girl is being evaluated again at 14 months of age for skin lesions (Fig. 2.2) and persistent oral thrush. Immunologic studies are similar to the first study, including IgG 1,370 mg/dL, IgM 86 mg/dL, IgA 88 mg/dL, and IgE < 10 IU/mL. No in vitro proliferative response to *Candida* spp. was detected. No autoimmunity could be demonstrated. No cardiac malformation or hypocalcaemia were present.

- Q3. Which of the following is the most likely diagnosis?
- A. Chronic mucocutaneous candidiasis (CMC)
 - B. SCID
 - C. DGS
 - D. HIES



Fig. 2.2 Skin lesions with *Candida albicans* in the biopsy at 14 months of age

Answer: The correct answer is A.

The persistence of systemic *Candida albicans* despite relative good T and B cell responses is crucial in the definition of a specific defect to this infection. In these cases, bacterial and viral infection can also be present. Most probably several not well-defined immunologic abnormalities are responsible for the varied clinical manifestations and severity of the disease. Although some molecular defects have been described in patients with autoimmune manifestations, not all cases of CMC have a molecular diagnosis [45].

- Q4. Which of the following is helping in the diagnosis of chronic mucocutaneous candidiasis?
- A. Lymphocyte subsets analysis
 - B. T cell response to mitogens
 - C. T cell response to *Candida* antigen
 - D. IgG subclasses analysis

Answer: The correct answer is C.

In vitro lymphocyte proliferation to *Candida* antigen measured by H^3 -thymidine incorporation is the standard test to confirm the clinical diagnosis [46].

- Q5. Which of the following strategies could be used to evaluate the carrier status of the patient's mother or siblings for genetic counseling and family planning?
- A. Analysis of memory B cells
 - B. IL-2 receptor mutation analysis
 - C. *AIRE* and *STAT1* mutations analysis
 - D. None

Answer. The correct answer is D.

Although most cases of CMC are sporadic and no mutations can be found, molecular defects in some forms of the disease have been recently described (with autoimmunity or autosomal dominant forms) [47].

Fig. 2.3 Persistent *Candida* infection at 27 years of age



This patient is now 27 years old and has some bacterial respiratory infections and persistent *Candida* infections in the fingers, esophagus, and urinary tract despite intensive antifungal therapy (Fig. 2.3). The *Candida* infection is resistant to itraconazole, ketaconazole, and fluconazole. She is now receiving voriconazole with good response to therapy. No endocrinopathy has been detected. No mutations have been demonstrated, although she has a low number and function of Th17 cells.

Practical Points

- The differential diagnosis of SCID must be established with analysis of lymphocyte subsets, T cell proliferation, and immunoglobulin levels.
- Clinical demonstration of *Candida* spp. infection is necessary, and the known molecular defects of PIDs associated with candidiasis must be ruled out.
- Intensive and permanent therapy with antifungal drugs is necessary. Studies of antifungal sensitivity in vitro are useful to adapt the most effective protocol. New and potent drugs have been developed.
- Other infections can also present and receiving the necessary antibiotic therapy facilitates the proliferation of *Candida*. Thus, close follow-up and repeated cultures of different body fluids must be performed.

Case 2.6 with Diarrhea and Erythrodermia

Presented by Isil B. Barlan and Elif Aydinler

A 3-month-old girl is presented with recurrent fever and diarrhea since 2 weeks of age. She developed pyoderma and erythrodermia at 2.5 months old. She was admitted with an abscess on her buttock and erythematous skin lesions. Her family

history reveals parental consanguinity. Physical examination demonstrates hepatosplenomegaly, alopecia, and *Pseudomonas aeruginosa* septicemia during admission. Initial laboratory evaluation shows eosinophilia ($1,500/\text{mm}^3$) and mild anemia. Immunological analyses reveal serum IgA $< 24.5 \text{ mg/dL}$, IgG 112 mg/dL , IgM $< 21 \text{ mg/dL}$, and IgE $9,000 \text{ IU/mL}$ with normal numbers of CD3^+ T cells 63 %, CD4^+ T cells 40 %, CD8^+ T cells 28 %, and absence of CD19^+ 0 % and CD20^+ 0 % B cells.

- Q1. What is the most likely diagnosis?
- A. Severe atopic dermatitis (AD)
 - B. Omenn syndrome (OS)
 - C. HIES
 - D. Netherton syndrome

Answer: The correct answer is **B**.

OS is a form of SCID characterized by erythrodermia, hepatosplenomegaly, lymphadenopathy, and alopecia. In patients with OS, B cells are absent, T cell counts are normal to elevated, and T cells frequently express a restricted T cell receptor (TCR) repertoire [48, 49].

Severe atopic dermatitis is a chronic, inflammatory skin disease characterized by a relapsing-remitting course. Although elevated serum IgE level is a commonly detected feature of this disease, lymphocyte immunophenotyping does not reveal absence of B cells [50].

HIES is a combined PID characterized by atopic dermatitis associated with extremely high serum IgE levels and susceptibility to infections. Like atopic dermatitis, an absence of B cells is not present in patients with HIES [51].

Netherton syndrome is caused by mutations in serine protease inhibitor Kazal type 5 (*SPINK5*). It is inherited as an autosomal recessive trait characterized by congenital ichthyosis, bamboo hair, and atopic diathesis. Recent studies showed reduced memory B cells and defective responses to vaccination, but not absence of B cells [52].

- Q2. Which of the following does not cause the clinical picture mentioned above?
- A. *RAG1*
 - B. *IL-7R*
 - C. *Artemis*
 - D. *ZAP-70*

Answer: The correct answer is **D**.

OS is classically caused by *RAG1* and 2 mutations but also reported in a growing list of other leaky SCID with mutations in components of mitochondrial RNA processing endoribonuclease, ADA, IL-2 receptor gamma, IL-7 receptor alpha, Artemis, and DNA ligase 4 [53, 54].

Mutations in *ZAP-70* lead to both abnormal thymic development and defective T cell receptor signaling of peripheral T cells. In contrast to lymphopenia present in the majority of patients with SCID, *ZAP-70*-deficient patients have lymphocytosis, despite the selective absence of CD8^+ T cells [54].

- Q3. Graft versus host disease (GVHD) may cause a similar clinical presentation as in OS. Which of the following is not true for differentiation of materno-fetal GVHD from OS?
- A. The inflammation in OS is triggered by predominantly clonally expanded Th1 cells.
 - B. Materno-fetal GVHD is commonly a fatal condition occurring in patients with SCID.
 - C. Y-chromosome positivity in the analysis of DNA extracted from skin biopsies of a male patient indicates the lack of maternal T cell engraftment.
 - D. If the analysis of skin biopsy DNA from a male patient reveals absence of the Y chromosome, infiltration of maternal cells and materno-fetal GVHD is confirmed.

Answer: *The correct answer is A.*

The inflammation observed in patients with OS is believed to be triggered by clonally expanded T cells, which are predominantly of the T helper type 2. These abnormal T cells, in the absence of proper regulation by other components of the immune system, secrete a host of cytokines that promote autoimmune as well as allergic inflammation [53].

Materno-fetal GVHD is commonly a fatal condition occurring in patients with SCID. Y-chromosome-specific PCR amplification analysis of DNA extracted from the skin biopsy is helpful to detect chimerical evidence of infiltrating maternal T cells in a male patient. Strong positivity for the Y chromosome indicates lack of maternal T cell engraftment, and thus confirming the diagnosis of OS. In contrast, Y-chromosome-specific PCR analysis of skin biopsy DNA from a male patient with a rash that is clinically and histologically typical of materno-fetal GVHD, reveals absence of the Y chromosome, indicating infiltration of maternal cells, and thus, confirming the diagnosis of materno-fetal GVHD [55].

- Q4. Which of the following is the most appropriate approach used for the definitive treatment of the patient mentioned above?
- A. IVIG replacement
 - B. Antibacterial medication
 - C. HSCT
 - D. Corticosteroids

Answer: *The correct answer is C.*

If untreated, patients with OS have a fatal prognosis. HSCT following an immunosuppressive regimen improves the outcome in OS. IVIG replacement and antibacterial medication are adjunctive therapies to treat infections. Corticosteroids are mainly used for the patients erroneously diagnosed as severe atopic dermatitis [53].

- Q5. Which of the following symptoms may not be related to infiltration of oligoclonally expanded T cells in OS?
- A. Alopecia
 - B. Diarrhea
 - C. Erythrodermia
 - D. Abscess

Answer: *The correct answer is D.*

Alopecia, diarrhea, and erythrodermia are caused by infiltration of oligoclonally expanded T cells, confirmed by biopsy and histological examination. As a proof, in RAG2 (R229Q/R229Q) mutant mice, a murine model of OS, expanded oligoclonal T cells, absence of circulating B cells, and peripheral eosinophilia is demonstrated. In addition, activated T cells infiltrated gut and skin, causing diarrhea, alopecia, and severe erythrodermia [56].

Practical Points

- OS is a form of SCID characterized by erythrodermia, hepatosplenomegaly, alopecia, lymphadenopathy, eosinophilia, and high serum IgE levels.
- In patients with OS, B cells are usually absent; T cell counts are normal to elevated; T cells are frequently activated and express a restricted TCR repertoire.
- The inflammation observed in OS is triggered by clonally expanded T cells, which are predominantly of the T helper type 2.
- Y-chromosome-specific PCR amplification analysis of DNA extracted from the skin biopsy is helpful to detect chimerical evidence of infiltrating maternal T cells in OS.
- HSCT following an immunosuppressive regimen improves the outcome in OS.

Case 2.7 with Pneumonia and Erythrodermia

Presented by Isil B. Barlan and Elif Aydinler

A 5-month-old girl with a history of recurrent fever and erythematous skin lesions presents to the emergency department. She had been well until the age of 3 months, when she developed severe pneumonia unresponsive to antibiotics. She is born to consanguineous parents with a family history of a dead sibling with a similar history. Physical examination shows bilateral crackles on chest auscultation, erythrodermia, hepatosplenomegaly, and absence of tonsils with no lymphadenopathy. Laboratory data include absolute lymphocyte count of 2,500/mm³, eosinophils 900/mm³, serum IgG 772 mg/dL, IgA 25 mg/dL, and IgM 88 mg/dL and IgE 2,000 IU/mL. Lymphocyte subsets analysis reveals CD3⁺ T cells 80 %, CD4⁺ T cells 70 %, CD8⁺ T cells 1 %, CD19⁺ B cells 14 %, and CD16⁺,56⁺ NK cells 1 %.

- Q1. What is the most likely diagnosis?
- A. SCID due to ADA deficiency
 - B. OS
 - C. HIV infection
 - D. SCID due to ZAP-70 deficiency

Answer: *The correct answer is D.*

Infants with SCID usually present with infections that are secondary to the lack of T cell function such as PCP, systemic candidiasis, generalized herpetic infections, and severe FTT secondary to gut infectious diarrhea. SCID diseases are usually classified according to the presence or absence of lymphocyte subsets (Table 2.1). Such a classification provides clues to define the underlying genetic defects.

X-linked T-B⁺ SCID (X-SCID) is the most commonly reported form of SCID. Autosomal recessive forms of T-B⁺ SCID are due to mutations in JAK3, deficiencies or abnormalities of CD3 subunits, and IL-7 receptor α -chain [57]. The molecular defects producing a T-B⁻ SCID phenotype include ADA deficiency, *RAG1/RAG2* mutations, and defects in the *Artemis* gene [58].

In contrast to lymphopenia present in the majority of patients with SCID, ZAP-70-deficient patients have lymphocytosis, despite the selective absence of CD8⁺ T cells. The clinical presentation is usually before 2 years of age with typical findings of SCID [54]. They present as healthy looking wheezy infants or can come to clinical attention for the eczematous skin lesions simulating atopic dermatitis with eosinophilia and elevated IgE similar to OS.

OS is a form of SCID characterized by erythrodermia, hepatosplenomegaly, lymphadenopathy, and alopecia. In patients with OS, B cells are absent, T cell counts are normal to elevated, and T cells are frequently activated and express a restricted T cell receptor repertoire [48, 49].

HIV infection heavily compromises the immune system. The decrease of the CD4⁺ T cell subset leading to AIDS has been considered as a hallmark of HIV infection [59].

- Q2. What is the risk for the next child to have the same disease as this patient (Fig. 2.4)?
- A. 75 %
 - B. 50 %
 - C. 25 %
 - D. 100 %

Answer: *The correct answer is C.*

ZAP-70 deficiency is reported to be inherited as an autosomal recessive trait [54, 60]. Since both parents would be carrying the mutant gene, the risk of having the disease for the next child would be 25 %; the risk of being a carrier would be 50 %. Therefore, the probability of having a healthy child who is not a carrier is 25 %.

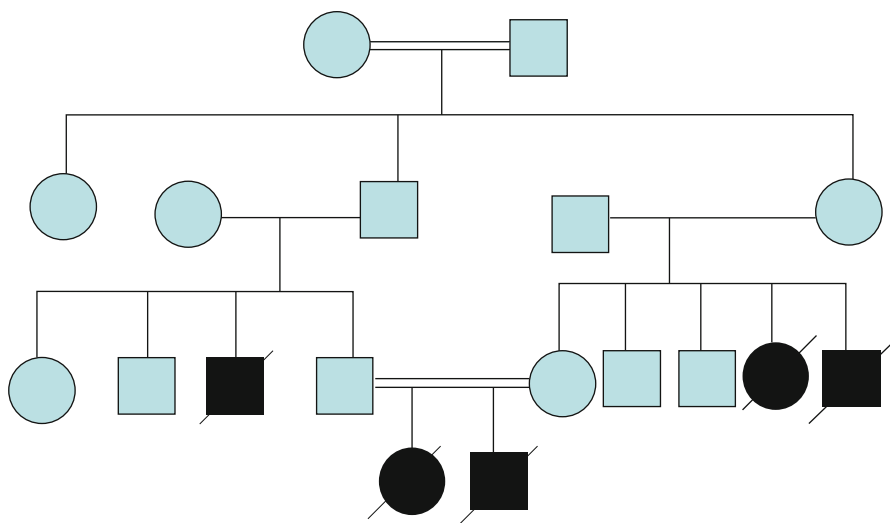


Fig. 2.4 Pedigree of Case 2.7 with pneumonia and erythrodermia

Q3. Which of the following is not considered in the management of this patient?

- A. HSCT
- B. Antibacterial medication
- C. IVIG
- D. Gene therapy

Answer: The correct answer is **D**.

IVIG replacement, antibacterial medication, and HSCT are considered in the management of all kinds of SCID. Gene therapy is considered for ADA deficiency and X-SCID [18].

Practical Points

- Pediatric patients affected by SCID are at greater risk of specific infections and FTT due to the impairment of T cell function.
- While most of the SCID patients have lymphopenia, ZAP-70-deficient patients have lymphocytosis in spite of the selective absence of CD8⁺ T cells.
- ZAP-70-deficient patients can present before 2 years of age with typical clinical manifestations of SCID. In addition, they may be misdiagnosed as OS since eczematous skin lesions with eosinophilia and elevated IgE may be seen in both disorders.
- ZAP-70-deficiency has an autosomal recessive pattern of inheritance.
- IVIG replacement, antibacterial medication, and HSCT are recommended in the management of all kinds of SCID.

Case 2.8 with Pneumonia and Skin Ulcers

Presented by Shabnam Pourhamdi and Asghar Aghamohammadi

The patient presented is a 12-year-old boy and the only child of consanguineous parents. He was healthy until 4 years of age when he began to develop recurrent episodes of rhinitis and otitis media. At the age of 10, he developed episodes of bacterial pneumonia and high-resolution CT scan (HRCT) showed bronchiectasis. Two years later, he developed asymmetrical skin leg ulcers. Immunologic studies showed normal levels of B cells and NK cells and low percentage of CD8⁺ T lymphocytes. The immunoglobulin levels were elevated: IgG 1,350, IgA 220, and IgM 276 mg/dL. Flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) showed decreased surface MHC class I expression compared to healthy controls.

- Q1. Which of these disorders should be considered in differential diagnosis of this clinical presentation.
- A. Cystic fibrosis (CF)
 - B. Wegener's granulomatosis (WG)
 - C. Common variable immunodeficiency (CVID)
 - D. Primary ciliary dyskinesia (PCD)
 - E. All of the above

Answer: *The correct answer is E.*

MHC class I (TAP1/2) deficiency is a rare disorder characterized by low expression of MHC class I molecules. It has a wide spectrum of clinical manifestations varying from no symptoms to severe ones, and it can be fatal due to respiratory failure. Symptomatic cases usually present with recurrent upper respiratory tract infections (such as rhinitis, otitis media, and sinusitis). The usual onset of these presentations is at late childhood, around 4–7 years of age. Later, they develop lower respiratory tract infections and chronic inflammatory lung diseases like bronchiectasis, bacterial pneumonia, and emphysema. About half of the cases develop local necrotizing granulomatous lesions, usually on the legs, that can progressively extend and ulcerate. Their HLA genotype is mostly homozygous, and they usually have related parents [61].

There are several other systemic disorders that may present with recurrent respiratory tract infections, granulomatous skin involvement, or both. So they should be considered in the differential diagnosis of MHC class I deficiency [62].

WG is a granulomatous inflammatory disorder involving the upper respiratory tract, lungs, and kidneys. Also it may present with granulomatous skin lesions [63]. It is very important to distinguish MHC class I deficiency from WG because patients with MHC class I deficiency do not respond to immunosuppressive therapy, that is, a treatment of choice in WG [62]. Bronchiectasis raises the suspicion of MHC class I deficiency but is not often developed during the course of WG. Negative c-ANCA,

absence of glomerulonephritis, and low surface expression of MHC class I are other helpful findings to exclude WG in these patients [64].

CF and PCD are autosomal recessive disorders with respiratory manifestations mimicking MHC class I deficiency [62]. Normal sweat chloride concentration and normal ciliary apparatus confirmed by electron microscopy exclude CF and PCD, respectively.

Granulomatous disease and bronchiectasis can also be the clinical manifestations of some PIDs, such as CGD and CVID. These disorders can be distinguished from MHC class I deficiency by serum electrophoresis, FACS analysis for MHC class I, and phagocyte function tests [65–68].

- Q2. Which laboratory finding cannot be observed in patients with MHC Class I deficiency?
- A. A gene mutation in *TAP1/TAP2* or *Tapasin*
 - B. Reduced CD8⁺ TCR α/β ⁺ T cells
 - C. Normal NK cell cytotoxic activity
 - D. Hypergammaglobulinemia

Answer: *The correct answer is C.*

MHC class I molecules have a critical role in antiviral immune response by presenting endogenous peptides to CD8⁺ T cells. For membrane expression, MHC class I molecules need to be loaded by peptides produced by degradation of endogenous proteins. The peptide loading of MHC class I heavy chain/ β 2 microglobulin heterodimer occurs in endoplasmic reticulum (ER) and needs the TAP1/TAP2 complex on the ER membrane that transports peptides [69]. Tapasin facilitates this loading with high affinity [70, 71]. Therefore, mutations in genes coding TAP1, TAP2, or Tapasin can result in reduced expression of MHC I.

T cell counts are normal in most patients; however, they usually show a reduction in the level of CD8⁺ TCR α/β ⁺ T cells. NK cells are in the normal range but have poor cytotoxic activity against MHC class I-deficient targets. Although hypergammaglobulinemia is detected in most cases, some patients could present with hypogammaglobulinemia [72, 73].

- Q3. The treatment options mentioned below should be considered in cases of MHC class I deficiency, except:
- A. Antibiotic therapy
 - B. Immunosuppressive treatment
 - C. IVIG
 - D. Lung transplantation
 - E. BMT

Answer: *The correct answers are B and E.*

Patients with MHC class I deficiency have respiratory manifestations similar to CF that can be managed with the same treatment modalities including antibiotic therapy and chest physiotherapy [62]. So when the diagnosis has been established, these

treatments should be also initiated to prevent bronchiectasis. Prophylactic antibiotic therapy should be considered in management of severe bronchiectasis.

It has been reported that IVIG in combination with antibiotics can be useful in some patients with severe pneumonia. Granulomatous skin lesions should be treated topically with antiseptics to reduce bacterial colonization. Immunosuppressive treatment may worsen skin lesions and respiratory symptoms and should not be administered. Lung transplantation could be a choice of treatment. BMT can lead to a severe GVHD mediated by donor NK cells [62].

Practical Points

- MHC class I deficiency is a rare disease that usually presents with recurrent upper and lower respiratory tract infections. Necrotizing granulomatous lesions are observed in near half of the cases.
- Systemic disorders such as WG, CF, and CVID that have similar clinical manifestations should be considered in the differential diagnosis.
- Gene mutations in *TAP1/TAP2* or *Tapasin*, reduction in CD8⁺ TCRα/β⁺ T cells and NK cell cytotoxic activity, and hypergammaglobulinemia are common laboratory findings in this disorder.
- Respiratory infections in MHC class I deficiency are usually caused by *Haemophilus influenzae*.
- Antibiotic therapy, IVIG, and lung transplantation are recommended treatment options in the management of MHC class I deficiency.

Case 2.9 Recurrent Interstitial Pneumonia and Failure to Thrive

Presented by Martha M. Eibl and Hermann M. Wolf

A 3-year-old boy presented is a second child of healthy, young and unrelated parents of Austrian origin and born at term after an uneventful pregnancy with normal birth weight. The family history did not reveal any problems. At the age of 4 months, the boy developed paronychia, which did not improve despite adequate therapy. Soon afterwards, chronic *Candida* spp. infection developed in the oral cavity. At 6 months of age, the patient was admitted to the intensive care unit in a critical condition with interstitial pneumonia complicated by bilateral pneumothorax, which required assisted ventilation. Hypogammaglobulinemia was diagnosed (IgG 28 mg/dL, IgM 230 mg/dL, IgA undetectable) and the patient received IVIG treatment with trough levels of about 500 mg/dL. Despite this therapy, 1 year later, a second attack of interstitial pneumonia (*Pneumocystis jirovecii*) complicated the course with iron deficiency anemia and failure to thrive with chronic diarrhea. Lymphocyte subset analysis revealed reduced CD4⁺ T cells, increased percentage of CD8⁺ T cells, and normal numbers of CD3⁺ T cells, B cells, and NK cells. T cell proliferative response was normal to mitogens (PHA, Con-A), but absent to recall antigen (Tetanus toxoid), despite repeated vaccinations. HLA-DR expression on lymphocytes was undetectable.

Biopsy of the small intestine revealed atrophy of the mucosa resembling celiac disease. Treatment with a gluten-free diet did not improve the condition and total parenteral nutrition had to be started.

Q1. What is the most likely diagnosis?

- A. MHC class II deficiency
- B. SCID
- C. HIGM
- D. XLA

Answer: *The correct answer is A.*

The combination of FTT, life-threatening infections with opportunistic organisms, poor response to treatment, hypogammaglobulinemia, and severe antibody deficiency, as well as decreased CD4⁺ T cells and increased CD8⁺ T cells, are indicative of a certain form of CID characterized by deficient expression of MHC class II molecules. The clinical phenotype of this form of CID varies from SCID-like presentation to mild symptoms (e.g., recurrent respiratory and/or bacterial infections) in patients with incomplete defects in MHC class II expression [74, 75].

MHC class II molecules are normally expressed on B cells; cells of the monocyte/macrophage lineage, such as antigen presenting cells (APC); and activated T cells. In patients with MHC class II deficiency, a regulatory defect in MHC class II transcription is present at the molecular level. Up to now, none of the patients described had a mutation in one of the MHC class II genes, HLA-DR, -DP, -DQ alpha and beta chain. Several transcription factors are essential for the expression and upregulation of MHC class II on hematopoietic and other cells. Mutations in four different transcription factors have been identified (three of them are DNA binding proteins: RFXANK, RFXAP, RFX5 and one is the transcriptional coactivator CIITA) [76, 77]. In most of the cases, mutation in one of those factors led to a defect in coordinated expression of all MHC class II genes, both constitutive and induced. T cells from these patients can be activated by mitogens and alloantigens, express activation markers (e.g., CD25), but unlike normal T cells, fail to express MHC class II. A defect in MHC class II-dependent antigen presentation explains the observed impairment of cell-mediated and humoral immunity despite normal number of APC.

Q2. For the above mentioned case, which of the following approaches could lead to a definitive diagnosis?

- A. Determination of serum immunoglobulins
- B. Determination of circulating B cells
- C. Lymphocyte phenotype analysis including expression of MHC class II
- D. Lymphoproliferative response to mitogens and recall antigens

Answer: *The correct answers are C and D.*

Definitive diagnosis of MHC class II deficiency, as demonstrated by lack of expression of the protein (HLA-DR), is confirmed by molecular analysis of the respective regulatory genes. Molecular diagnosis is mandatory for definitive diagnosis in patients with an incomplete phenotype [76].

Because of the severe clinical situation in the patient described, SCID has been suspected and HSCT has been discussed. HLA haplotypes were examined in the patient and his family. The tissue-typing laboratory observed that while the patient, both parents and the healthy brother, could be typed for HLA-A, B, and C, typing for HLA-DR was inconclusive for the patient. The test was repeated as they could not interpret the observation.

Because of the interstitial pneumonia in the patient and the severely decreased IgG and IgA with high IgM, the differential diagnosis of HIGM has also been raised. Low numbers of CD4⁺ T cells did not fit this diagnosis. The absence of HLA-DR, as determined by lymphocyte phenotyping, proved a defect in MHC class II expression. Absent response to recall antigens indicated defective function and further clarified the picture. For this reason, examination of MHC class II expression on lymphocytes is a helpful addition to the basic screening of patients with suspected CID.

- Q3. Which PIDs other than MHC class II deficiency predispose a patient to interstitial pneumonia caused by *Pneumocystis jirovecii* infection?
- A. HIGM
 - B. XL-SCID
 - C. Selective antibody deficiency with/without IgG subclass deficiency
 - D. Chronic granulomatous disease (CGD)

Answer: The correct answers are **A and B**.

Protective immune response to facultative intracellular organisms, such as *Pneumocystis jirovecii*, requires an intact T cell immunity and is a characteristic clinical problem in patients with severe T cell abnormalities [78]. Furthermore, CD40-CD40L interaction, defective in patients with HIGM, is also essential for protection against infections with these opportunistic pathogens. This explains the poor prognosis of patients with HIGM due to defective CD40-CD40L interaction as compared to other forms of PIDs with impaired immunoglobulin class switching [79–81].

- Q4. What are the treatment options for patients with MHC class II deficiency?
- A. Immunoglobulin substitution therapy only
 - B. Prophylactic antibiotics only
 - C. HSCT
 - D. Vaccination with attenuated live virus vaccines

Answer: The correct answer is **C**.

While IVIG therapy and prophylactic antibiotic treatment have to be initiated immediately after diagnosis, curative treatment can only be achieved by HSCT [82]. When patients with MHC class II deficiency have a histoidentical sibling donor, the outcome of HSCT is usually very good; however, in all other cases the prognosis varies [83].

The patient presented had a histoidentical healthy brother who donated bone marrow and the patient was cured.

Practical Points

- Determination of MHC class II (HLA-DR) expression on lymphocytes by flow cytometry should be included in the screening examination for CID.
- Siblings of patients with MHC class II deficiency should be investigated if possible before live vaccines are given because in rare cases, patients with this deficiency can be asymptomatic in early childhood as genotype-phenotype correlation can vary, and still be jeopardized by live vaccines.
- Considerations for treatment will have to take into account the clinical situation of the patient.

Case 2.10 with Autoimmune Thrombocytopenia, Developmental Retardation, and Dysmorphic Phenotype

Presented by Andrea Martín and Pere Soler-Palacín

A 3-year-old girl presented with autoimmune thrombocytopenia (ITP) refractory to conventional therapies and was ultimately treated with splenectomy. Other clinical features were hypotonia and mild developmental retardation present since the first months of life, a dysmorphic phenotype (short philtrum and cleft palate), and a mild congenital atrial septal defect that had not yet been corrected. During the first 2 years of life, she had several episodes of acute otitis media and upper and lower respiratory tract infections. There was no consanguinity or history of PID in her family. Immunologic studies were performed with the following results: WBC 7,000/mm³ (neutrophils 4,480/mm³, lymphocytes 560/mm³, monocytes 840/mm³, eosinophils 980/mm³), IgG 900 mg/dL, IgA < 10 mg/dL, IgM 1,450 mg/dL with poor response to vaccines (both protein and polysaccharide antigens), and IgE 21 IU/mL. Lymphocyte subsets by flow cytometry showed CD3⁺ T cells 54.4 % (absolute count of 305/mm³), CD4⁺ T cells 34 % (absolute count of 190/mm³), CD8⁺ T cells 20 % (absolute count of 113/mm³), CD19⁺ B cells 27 % (absolute count of 151/mm³), and CD56⁺ NK cells 18.3 % (absolute count of 102/mm³). Proliferative response to mitogens was normal.

- Q1. Which is the most likely diagnosis?
- A. Hyper IgM syndrome (HIGM)
 - B. Selective IgA deficiency (SIgAD)
 - C. DiGeorge syndrome (DGS)
 - D. Specific antibody deficiency (SAD)

Answer: *The correct answer is C.*

Although DiGeorge syndrome (DGS) is classically defined as a congenital T cell immunodeficiency associated with congenital heart defects and hypocalcaemia and is usually diagnosed in the perinatal period, its phenotype is much more variable

and extensive [84]. In this case, the dysmorphic face, congenital atrial septal defect, neurological symptoms, and T cell deficiency raised the suspicion of this syndrome. Although defective T cell function is the hallmark of DGS, patients show a broad range of T cell counts and proliferative responses [85]. Autoimmune phenomena have been extensively described in this syndrome [86]. Later, a microdeletion at 22q11 was confirmed by mutational analysis in this case.

The most important laboratory criteria for the diagnosis of HIGM are low serum IgG, IgA, and IgE concentrations (not present in our patient) and normal or elevated serum IgM levels. Autosomal forms are due to *AID* or *UNG* mutations, both of which were excluded in this patient by mutational analysis [80].

SIgAD is defined by low IgA levels in a patient older than 4 years with normal IgG and IgM levels and no other causes of hypogammaglobulinemia and is sometimes associated with polysaccharide antigen unresponsiveness [87]. Although the laboratory data revealed undetectable plasma IgA levels, and autoimmune cytopenia has been described in SIgAD, major malformations and such severe lymphocytopenia have not been reported in this entity. In addition, an increased prevalence of IgA deficiency in patients with DGS has been described [88].

SAD is characterized by normal concentrations of immunoglobulins, which was not the case in this patient, normal IgG subclasses, and poor IgG antibody response to the majority of polysaccharide antigens, with increased susceptibility to recurrent bacterial infections [89]. As in SIgAD, dysmorphic features and lymphocytopenia have not been reported in isolated SAD.

- Q2. Which one is the diagnostic clue of DGS?
- A. T cell lymphopenia
 - B. 22q11 microdeletion
 - C. Congenital heart defects and hypocalcaemia
 - D. Poor response to polysaccharides antigens

Answer: *The correct answer is A.*

Although 22q11 microdeletion (present in 90 % of patients), congenital heart defects, and hypocalcemia are common features in DGS and support its diagnosis, it can only be diagnosed if moderate to severe lymphopenia is present when associated with other clinical and analytic features [90]. Otherwise, only the diagnosis of a 22q11 microdeletion syndrome can be established and the patient should not be considered as immunocompromised.

Both ESID and PAGID have reported diagnostic criteria for both partial and complete forms of DGS (Table 2.2), with complete forms accounting for less than 1 % of total DGS patients. Our patient fulfills the diagnostic criteria for definitive partial DGS [87, 91, 92].

Most DGS patients have normal antibody function; but impaired specific response to polysaccharide antigens has also been described [93], though it is not considered as a diagnostic criterion of DGS.

At the age of 13 years, the patient presented persistent fever and right knee swelling and the diagnosis of a juvenile rheumatoid arthritis-like syndrome was

Table 2.2 Diagnostic criteria for both partial and complete DiGeorge syndrome [87]

Partial DiGeorge syndrome	Definitive	Reduced CD3 ⁺ T cells (less than 500/mm ³) during the first 3 years of life and one of the following: Conotruncal cardiac defect and laboratory or clinically manifested hypocalcaemia Conotruncal cardiac defect and deletion of chromosome 22q11.2 Laboratory or clinically manifested hypocalcaemia and deletion of chromosome 22q11.2 Conotruncal cardiac defect and laboratory or clinically manifested hypocalcaemia and deletion of chromosome 22q11.2
	Probable	Reduced CD3 ⁺ T cells (less than 1,500/mm ³) during the first 3 years of life and deletion of chromosome 22q11.2
	Possible	Reduced CD3 ⁺ T cells (less than 1,500/mm ³) during the first 3 years of life and at least one of the following: Cardiac defect Laboratory or clinically manifested hypocalcaemia Dysmorphic facies or palatal abnormalities
Complete DiGeorge syndrome	Definitive	Reduced/absent CD3 ⁺ T cells (less than 50/mm ³) and all of the following: Athymia documented as fewer than 50 recent thymic emigrants (CD3 ⁺ CD45RA ⁺ CD62L ⁺ cells/mm ³) and/or TRECs < 100/100,000 T cells Hyperparathyroidism Heart defect

established. Treatment with oral leflunomide was started, with good clinical and analytical response.

- Q3. Which is the immunologic disorder leading to autoimmune diseases in DGS?
- A. DGS is not associated with an increased risk of autoimmunity.
 - B. Thymic output dysregulation.
 - C. IgA deficiency.
 - D. IVIG therapy.

Answer: The correct answer is **B**.
Impaired development of natural CD4⁺ CD25⁺ regulatory T cells and impaired thymic central tolerance may predispose to the development of autoimmunity in patients with DGS, and this abnormal thymic development seems to be the result of impaired expression of autoimmune regulator genes and other transcription factors [94].

Mainly autoimmune cytopenias, but also other clinical manifestations, such as juvenile rheumatoid arthritis-like polyarthritis or endocrinopathy (mainly affecting the thyroid gland), have been described [86, 93, 95–98].

As previously described, patients with DGS can present with both SIgAD and impaired antibody production, and the need of intravenous/subcutaneous immunoglobulin has been reported in some cases [93]. Obviously, these two features do not play a role in the occurrence of autoimmune disorder in DGS patients.

Q4. Which of the following are therapeutic options in DGS?

- A. Thymic transplantation for complete forms
- B. Heart surgery if needed
- C. HSCT for complete forms
- D. All of them

Answer: *The correct answer is D.*

A major cause of death in patients with DGS is described to be congenital heart defects; therefore, prompt and adequate surgical treatment is mandatory [99].

A progressive increase in the number of CD3⁺ T lymphocytes has been reported for the vast majority of patients with partial DGS, so neither TT nor HSCT is indicated in these cases [16]. However, complete DGS should be considered as a SCID since outcome is poor without a curative treatment, with most patients dying before the age of 2 years [100]. Two therapeutic approaches have been described: Thymic transplantation [101] and BMT and peripheral blood T cell transplantation from HLA-matched sibling donors. HSCT provides long-lasting immunity when mature T cells are included in the donor cells and is a suitable and more available alternative to thymic transplantation, but a long-term survival has been reported in 36 out of 50 patients with complete DGS treated with thymic transplantation, with the development of naive T cells and a diverse T cell repertoire [101].

Practical Points

- Atypical forms of DGS should be born in mind in patients with T cell immunodeficiency and characteristic clinical features, even in older patients.
- Moderate to severe T cell lymphopenia is the diagnostic clue of DGS in patients with typical clinical manifestations.
- In addition to recurrent infections, both autoimmune phenomena and lymphoproliferative disorders have been described in DGS, mainly due to thymic output dysregulation.
- Although uncommon, complete DGS should be promptly diagnosed and treated since outcome is poor without adequate therapy. Both thymic transplantation and HSCT are therapeutic options in this setting when mature T cells are included in the graft.

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