Index of Suspicion
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Case 1 Presentation
A 12-month-old girl who has trisomy 18 presents with 3 weeks of intermittent fever, emesis, and irritability, but no diarrhea, rash, lethargy, or seizure activity. In addition, she has lost nearly 300 g over the previous 3 months. Her medical history includes repair of tetralogy of Fallot, first-degree atrioventricular block, chronic lung disease, seizures, and gastroesophageal reflux. Medications include phenytoin and inhaled corticosteroids.

Physical examination reveals a small, irritable, dysmorphic child who has a temperature of 101.1°F (38.4°C) and blood pressure of 122/57 mm Hg. Height, weight, and head circumference are below the third percentile. There is a 3/6 systolic regurgitant murmur. Abdominal examination is limited due to pacemaker placement in the right upper quadrant, but the liver is palpated 3 cm below the costal margin and spleen at 2 cm. The remainder of the physical findings are normal.

CBC is normal except for a WBC count of 18.5×10^9/mcL (18.5×10^9/L) and platelet count of 806.0×10^9/mcL (806.0×10^9/L). Blood chemistry results, including a standard liver panel that includes concentrations of total protein and albumin, are normal. Urinalysis reveals mild proteinuria and hematuria, and the CSF is normal. Initial blood cultures grow Streptococcus viridans. The fever and bacteremia resolve with intravenous antibiotic therapy, but the hypertension and irritability persist.

Subsequently, her right thigh becomes swollen and tender. A radiograph reveals severe osteopenia and a femur fracture. A skeletal survey demonstrates diffuse osteopenia, as well as old pathologic fractures of both radii and ulnae and some ribs. Additional laboratory evaluation reveals mild hypothyroidism (thyroid-stimulating hormone of 11.2 mIU/mL, free thyroxine of 1.03 ng/mL [13.3 pmol/L]). Concentrations of parathyroid hormone, insulin-like growth factor, morning cortisol, dihydroxyvitamin D, 25-hydroxyvitamin D, calcium, ionized calcium, phosphorus, and alkaline phosphatase are normal. An imaging study reveals the underlying cause of the osteopenia and hypertension.

Case 2 Presentation
A healthy 8-month-old girl presents to the ED with a 2-day history of a temperature as high as 103.0°F (39.5°C). Over the past 12 hours, she has become progressively fussier and difficult to console. Her appetite has diminished significantly over the past 24 hours without any change in her urine output. She has had no congestion, rhinorrhea, cough, respiratory distress, vomiting, diarrhea, hematochezia, abnormal rash, joint swelling, abdominal distention, or drawing up of her legs.

On physical examination, the infant does not appear toxic and although fussy, is consoled easily when held. Her temperature is 100.9°F (38.3°C), respiratory rate is 38 breaths/min, heart rate is 111 beats/min, and blood pressure is 91/60 mm Hg. The physical findings are normal except for the abdominal examination. Although her abdomen is soft, the infant pushes away the examiner’s hand. No abnormal masses or organomegaly are palpated.

Her WBC count is 11.8×10^9/mcL (11.8×10^9/L), with 38% lymphocytes and 55% neutrophils. Urinalysis yields normal findings. The CSF contains 1 erythrocyte, 1 WBC, and normal concentrations of glucose and protein.

She is started on antibiotics empirically and admitted to the hospital.

Frequently Used Abbreviations

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<tr>
<th>Abbreviation</th>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>BUN</td>
<td>Blood urea nitrogen</td>
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<td>CBC</td>
<td>Complete blood count</td>
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<td>Central nervous system</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>ECG</td>
<td>Electrocardiography</td>
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<td>ED</td>
<td>Emergency department</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<td>GU</td>
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<td>WBC</td>
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Case 3 Presentation

Since 5 months of age, an 11-year-old girl has suffered from atopic dermatitis characterized by dry, scaly, pruritic skin. She has been treated with topical steroids, emollients, and several courses of oral steroids, but has never had a period of time when her skin condition was under good control. She has been hospitalized several times for secondary bacterial infections of her skin, including erythroderma. She also has experienced mild intermittent asthma and multiple allergies to foods and environmental antigens. Both parents had atopic dermatitis when younger. She is exposed to cigarette smoke at home.

On physical examination, the girl’s height and weight are between the 10th and 25th percentiles, and her vital signs are normal. She has coarse facial features, with deep-set eyes, a wide nasal base with broad alar nasi, and thick ear cartilage. The skin at the corners of her mouth is dry and cracked. She has dry, scaly, erythematous, and lichenified skin from head to toe, with extensive scalp scaling. Multiple areas are excoriated, the worst being at her wrists and ankles, which have several fissures but no abscesses. There is hyperlinearity and peeling skin on her palms and soles. Her fingernails and toenails show a small amount of pitting and grooves. All other physical findings are negative.

Case 4 Presentation

An 11-week-old boy presents to the ED in December with a 3-day history of cough and congestion. He has had a temperature up to 101.0°F (38.4°C) at home but is feeding well, taking 5 oz of formula every 3 hours during the day, and having his usual number of wet diapers.

On arrival, the boy’s temperature is 102.2°F (39.0°C). He is deep suctioned and started on 1 L of oxygen via nasal cannula because of a respiratory rate of 60 breaths/min. Results of rapid testing for respiratory syncytial virus and influenza A and B antigens are negative, and a chest radiograph shows peribronchial thickening. After 1 hour, the boy still exhibits tachypnea but is not in respiratory distress. He is admitted to the hospital for observation.

On physical examination, the infant appears well developed and well nourished but is fussy when examined. His weight is 4.735 kg (10th percentile). He has mild nasal congestion. His respiratory rate is 55 breaths/min, and he has mild substernal retractions, but his breath sounds are clear. His oxygen saturation on room air is 100%. His heart rate is 168 beats/min. Other physical findings are normal.

After several hours, the boy’s respiratory rate increases to 80 breaths/min and his heart rate to 180 beats/min. He appears less active and refuses his bottle. He is mottled and lethargic and has a capillary refill of 4 seconds. He is given a 20 mL/kg intravenous bolus of normal saline. Laboratory testing reveals the diagnosis.

Case 1 Discussion

Abdominal ultrasonography was performed to evaluate for renal causes of hypertension and revealed a horseshoe kidney as well as two soft-tissue masses within the right upper region of the retroperitoneum. Doppler evaluation of the right renal hilum revealed an increased resistive index, likely caused by compression by the adjacent mass. Subsequent CT scan of the abdomen was difficult to interpret due to artifact from the pacemaker, but at least one portion of the visible mass appeared to arise from the caudate lobe of the liver.

Additional laboratory evaluation revealed a homovanillic acid value of 30.4 mg/g (normal, 0 to 27.9 mg/g), vanillylmandelic acid value of 30.0 mg/g (normal, 0 to 18.8 mg/g), and alpha-fetoprotein value of greater than 30,000 IU/mL (normal, 0.5 to 5.5 IU/mL). Serum catecholamine concentrations were normal. Biopsy of the mass revealed epithelial hepatoblastoma, and the second mass was determined to be a local metastasis, which was the only metastatic lesion detected.

The patient is undergoing chemotherapy in an effort to decrease tumor bulk. Repeat imaging will be performed after three cycles of chemotherapy. If the response to chemotherapy is favorable, surgical resection is planned.

The Finding

Abnormal bone mass density (BMD) occurs when the normal process of bone modeling or remodeling is disrupted. Bone remodeling involves three steps: production and maturation of organic matrix by osteoblasts, mineralization of the matrix, and subsequent resorption of the matrix by osteoclasts. Disruption of osteoblastic or osteoclastic activity changes the microarchitecture of the bone and results in low BMD, termed osteopenia. Osteoporosis is an extreme form of osteopenia, defined by a BMD of more than 2.5 standard deviations below the age-adjusted mean.
Abnormal mineralization results in osteomalacia. Osteomalacia occurs when quantities of calcium and phosphorus are insufficient to promote normal bone mineralization, either from nutritional deficiencies, as in vitamin D deficiency, or intrinsic disease (eg, renal tubular acidosis).

Osteopenia in the pediatric population is due most often to an underlying medical condition or exposure. Primary osteopenia is rare. A number of chronic diseases have been associated with osteopenia, including inflammatory bowel disease, celiac disease, cystic fibrosis, chronic renal disease, anorexia nervosa, neuromuscular disorders, hyperthyroidism, and malignancy. The mechanisms responsible for the osteopenia vary from condition to condition, but the result can be due to a combination of factors, such as delayed growth and maturation, malnutrition, immobilization, and exposure to inflammatory cytokines, which have been shown to increase osteoclastic activity.

In the case of malignancy, paraneoplastic syndromes also may cause abnormal BMD, as with hepatoblastoma. Some genetic disorders, such as osteogenesis imperfecta, affect the bone directly. Several medications, including corticosteroids and chemotherapeutic agents, can affect both osteoblastic and osteoclastic activity.

Osteopenia will not be evident on plain radiography until 30% of the bone mass is lost. For more sensitive measures of BMD, several methods of densitometry exist, which vary in exposure to radiation, cost, and other factors. Many consider dual-energy radiograph absorptiometry (DXA) the preferred method for use in children because it is fast, precise, safe, and more readily available. However, established guidelines for the use of DXA scanning in pediatric patients are few, and it is not always clear how the results of the screening should influence medical management.

Because osteopenia in pediatric patients often is a secondary problem, management should focus on identifying and treating the underlying illness or removing the negative exposure. In some cases, initiation of hormone therapy, treatment with bisphosphonates, administration of calcium, or vitamin D supplementation may be useful. Care should be taken to avoid musculoskeletal trauma until the bone density has improved. For children who have known risk factors for abnormal BMD, preventive efforts should be made to remove inciting factors and maximize nutritional status.

The Other Problem

Primary hepatic malignancies comprise fewer than 4% of all pediatric solid tumors. Hepatoblastoma is the most common primary hepatic tumor. Other malignant tumors such as hepatocellular carcinoma, infantile hemangioendothelioma, and angiosarcoma, as well as several benign lesions, occur less frequently.

Hepatoblastoma occurs most often in children younger than 3 years of age, with a median age of 18 months. It has been associated with several clinical conditions, congenital malformations, and syndromes, including Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and trisomy 18. Hepatoblastoma also has been associated inversely with low birthweight.

Histologically, there are two primary types of hepatoblastoma. Epithelial hepatoblastoma contains fetal cells, embryonal malignant cells, or an admixture, and mixed hepatoblastoma contains both mesenchymal and epithelial elements. Pure fetal cell tumors confer a more favorable prognosis. Rare subtypes of the epithelial form include macrotrabecular and small cell histology, the latter conferring a poorer prognosis.

Hepatoblastoma often presents as an asymptomatic abdominal mass or hepatomegaly. The tumor usually is unifocal and located in the right hepatic lobe. With progression, patients may experience weight loss, anorexia, vomiting, and abdominal pain. An elevated alpha-fetoprotein value is the classic laboratory finding, but anemia and thrombocytosis also occur commonly. The bilirubin and liver enzyme concentrations typically are normal. Osteopenia and associated pathologic fractures often are noted incidentally at the time of diagnosis, but usually are not the presenting sign. Up to 20% of patients have pulmonary metastases at presentation. Other, less common sites for metastatic disease include bone, brain, eye, and ovary.

Abdominal ultrasonography is an excellent tool for the radiographic diagnosis of hepatoblastoma. Computed tomography scan and magnetic resonance imaging are useful for surgical planning and disease staging. Due to the common presence of osteopenia and infrequency of metastatic bone disease, bone scanning is not useful.

Successful treatment of hepatoblastoma relies on complete surgical resection of the hepatic tumor. Adjuvant chemotherapy typically is used after complete resection. Preoperative chemotherapy frequently is used for larger tumors or for those initially deemed unresectable to shrink the tumor and allow for more extensive or complete resection.

The overall survival rate is approximately 70%. In the absence of metastatic disease, complete resection of the primary tumor confers a nearly 100% survival rate. When metastatic
disease is present or the primary tumor is not resected completely, the survival rate drops to less than 25%. Liver transplantation has been used to increase survival in patients who have high-grade hepatoblastoma.

This infant had several characteristics of hepatoblastoma at the time of presentation, including emesis, weight loss, hepatomegaly, and thrombocytosis. Twenty percent of children who have hepatoblastoma have thrombocytosis, which appears to be caused by excess production of thrombopoietin.

The association of osteopenia with hepatoblastoma has been reported, with osteopenia and pathologic fractures often being detected at the time the hepatoblastoma is diagnosed. (1)(2)(3)

The occurrence of osteopenia in this patient likely was multifactorial and related, in part, to other features of her complex medical condition, including immobility, poor nutrition, and exposure to medications associated with bone demineralization. Ultimately, the methodical search for an explanation of each of her abnormal findings led to the discovery of the occult tumor and subsequent therapy.

**Lessons for the Clinician**

Children who have chronic and complex medical illnesses have multiple risk factors for bone demineralization. In addition, primary endocrine disorders or other illnesses such as malignancy may lead to osteopenia in any child. Pediatricians caring for children who have complex medical issues must have a high degree of suspicion for osteopenia and pursue an aggressive and multidisciplinary diagnostic plan, realizing that occult malignancy is one condition associated with the bone disorder. (Jennifer Maniscalco, MD, MPH, Amy L. Dryer, MD, Asher Marks, MD, Megan Yunghans, MD, Children’s National Medical Center, Washington, DC)

**References**


**Case 2 Discussion**

The girl was admitted to the hospital because of fever with no apparent source and was presumed to have sepsis. Because of a difficult initial abdominal examination, she was re-examined 3 hours later while she slept. She awakened from sleep immediately upon palpation of her abdomen and cried vigorously for approximately 30 minutes. Abdominal ultrasonography was ordered immediately to evaluate for intussusception. No signs of intussusception were present, but a 1×2.4-cm cystic abnormality was noted in the right lower quadrant. In an older patient, this finding would be indicative of appendicitis, but because appendicitis is so rare at this age, a CT scan of the abdomen and pelvis without and with intravenous and rectal contrast was performed.

The scan confirmed the blind-ending tubular structure in the right lower quadrant that was suggestive of appendicitis. The girl immediately underwent laparotomy and was noted to have a perforated, suppurrative appendicitis. She continued to have fever while receiving broad-spectrum antibiotics for 4 days after the appendectomy. Repeat ultrasonography of the abdomen and pelvis at that time showed no signs of an abscess, and she defervesced. By the fifth day, the patient had been afebrile for 24 hours and was discharged from the hospital on oral antibiotics. She completed her antibiotic course without any additional problems.

**The (Mis)Diagnosis**

Although appendicitis is the most common surgical emergency in childhood, diagnosis often is delayed in children younger than 3 years of age. This delay is believed to result from two important factors. First, childhood appendicitis is most common in the second decade of life, making it a very uncommon cause of fever in children younger than 1 year of age. Second, symptoms and signs of appendicitis can be nonspecific, especially in younger children. Typical manifestations of appendicitis (in decreasing order of frequency) are abdominal pain, vomiting, fever, abdominal distention, and diarrhea. Signs on physical examination predominantly include fever and diffuse abdominal tenderness. However, the picture can vary substantially from patient to patient.

Because acute gastroenteritis (AGE) is much more common and can present the same clinical picture, most young children who have appendicitis receive an initial diagnosis of AGE. Intussusception also occurs in this age group and should be considered in the differential diagnosis. Appendicitis should be entertained when signs and symptoms persist despite adequate fluid resuscitation. By that time, most affected children have experienced appendiceal perforation. Difficulty in diagnosing appendicitis in infants and nonverbal very young children leads to the high rates of appendiceal perforation observed in this age group.
Evaluation
The history and physical examination are critical in the initial evaluation. Fever from no identifiable source in a child younger than 1 year of age most commonly is due to viral infection. However, clinicians concentrate on identifying those patients who have a bacterial infection because of serious complications if these infections are untreated. The most common bacterial infections are those of the urinary tract, bacteremia, pneumonia, meningitis, and osteomyelitis.

Once appendicitis is suspected, surgical consultation is warranted. The clinician can obtain ultrasonography of the abdomen, which has been shown to be very sensitive and specific for appendicitis. If physical examination and ultrasonography yield equivocal findings, CT scan of the abdomen and pelvis may be useful. Using this approach, multiple studies have shown an increase in sensitivity and specificity in diagnosing appendicitis in children compared with ultrasonography alone. Parents should be advised that CT scan involves the use of a significant amount of ionizing radiation.

Therapy
The definitive treatment for ruptured appendicitis is fluid resuscitation to a euolemic state, intravenous broad-spectrum antibiotics, and appendectomy. An alternative approach in the presence of an established, focal intra-abdominal abscess without peritonitis is to treat the child with intravenous antibiotics, drain the abscess percutaneously, and perform interval appendectomy 4 to 6 weeks later. Antibiotic regimens should cover common GI bacteria such as Escherichia coli, Enterococcus, and anaerobes; antibiotics generally are continued postoperatively until the intra-abdominal infection is resolved clinically.

Lessons for the Clinician
Appendicitis is the most common surgical abdominal emergency in childhood. Diagnosis can be a challenge, especially in a child younger than 1 year of age. Appendicitis often is misdiagnosed as AGE and treated as such. If the infant does not respond appropriately to fluid therapy and continues to have discomfort and fever, the clinician must consider appendicitis, and additional diagnostic evaluation is indicated. Delay in diagnosis can lead to a more complicated course and treatment and an increased hospital stay. (Stacy B. Pierson, MD, All Children’s Hospital, St. Petersburg, Fla.)

Case 3 Discussion
The differential diagnosis included the previous diagnosis of severe atopic dermatitis, severe seborrheic dermatitis or sebopsoriasis, and allergic contact dermatitis. However, the chronic course and severity of this patient’s recurrent cellulitis and abscesses prompted consideration of other unusual diagnoses, including Wiskott-Aldrich syndrome, hyper-immunoglobulin (Ig) E syndrome (HIES), congenital ichthyosiform erythroderma, Netherton syndrome, Leiner disease, and selective IgA deficiency, as well as other immunodeficiencies. Screening laboratory tests were ordered, including immunoglobulins, a CBC with differential count, and allergy testing.

Concentrations of serum immunoglobulins were as follows:

- IgE, 14,150.0 IU/mL (normal, 35.0 to 262.0 IU/mL)
- IgA, 187.0 mg/dL (normal, 35.0 to 420.0 mg/dL)
- IgG2, 1,070.0 mg/dL (normal, 609.0 to 2,626.0 mg/dL)
- IgM, 81.0 mg/dL (normal, 35.0 to 262.0 mg/dL)
- IgD, <1.0 mg/dL (normal, 0 to 14.0 mg/dL)

Her WBC was 9.6×10⁹/mcL (9.6×10⁹/L), with 12% eosinophils and 1.17×10⁹/mcL (1.17×10⁹/L) absolute eosinophils; Hgb was 13.8 g/dL (138.0 g/L); and platelet count was 497.0×10⁹/mcL (497.0×10⁹/L). Serum radioallergosorbent testing (RAST) for common tree, grass, and dust allergens often found in the northeastern United States (Northeast panel) and several foods revealed a marked response to all antigens tested.

The history, physical findings, and extremely high serum IgE values strongly suggested HIES. Serial testing of serum IgE in the following months revealed values of 28,099.0 IU/mL and 56,171.0 IU/mL. She was placed on a regimen of topical steroids and emollient as well as an antihistamine and antibiotic for presumed bacterial infection related to her flare.

Similar Disorders
Although this patient was diagnosed as having a rare condition, other, more common conditions, including atopic dermatitis, seborrheic dermatitis, and allergic contact dermatitis, may have similar presentations without the associated symptoms seen in HIES.

Atopic dermatitis is an inflammatory skin condition characterized by pruritus, a chronic course, and typical distribution for age, with a predilection for extensor surfaces in infants and flexural creases in children and adults. Chronic inflammation and scratching can lead to hyperpigmentation and lichenification. Allergens such as pollen, dander, dust, and foods and environmental conditions most often are the triggers. Histologic examination of the skin shows infiltration of lymphocytes...
and macrophages into the superficial dermis, with edema in the epidermis. There is a genetic predisposition to this condition, and there may be a personal history of asthma and allergic rhinitis.

Contact dermatitis also is an inflammation of skin in response to an antigen or an irritant. Allergic contact dermatitis is a delayed hypersensitivity reaction in which the skin previously has been sensitized to the allergen. Lesions usually appear within 1 to 4 days of exposure. Irritant contact dermatitis occurs when a substance, usually a chemical, produces a local cytopathic effect on the epidermis, with subsequent inflammation of the dermis. Clinically, contact dermatitis may present acutely with papules or fluid-filled vesicles (often in a linear pattern) on erythematous skin, at times with edema; subacutely with papules on an erythematous base; or as a chronic condition with scaling, lichenification, and even fissure formation. The dermis is infiltrated acutely and subacutely with lymphocytes and other mononuclear cells; chronic contact dermatitis is characterized by acanthosis and hyperkeratosis.

Seborrheic dermatitis affects areas of the skin that are rich in sebaceous glands. Clinically, patients present with pruritic erythematous patches and plaques that have distinct margins and that overlie greasy yellowish scales, most often seen in the scalp, eyebrows, nasolabial creases, chest, axilla, and groin. This condition frequently presents in infancy or after puberty. Although the pathophysiology is not understood completely, seborrhea is believed to be an inflammatory reaction to a skin yeast, *Pityrosporum ovale*. Treatment includes topical steroids and shampoos containing antifungal ingredients.

The Condition

HIES was reported initially in 1966 by Davis and associates and called Job syndrome. (1) The biblical book of Job records that “Satan... smote Job with sore boils from the sole of his foot unto his crown” (Job 2:7). This description was likened to the recurrent cold skin abscesses that afflict these patients. In 1972, Buckley and colleagues (2) further described a similar syndrome characterized by recurrent cutaneous and pulmonary abscesses, coarse facies, chronic dermatitis, elevated IgE concentrations, and eosinophilia, termed temporarily Buckley syndrome. These two syndromes later were found to be the same entity.

HIES is a multisystem disorder. Typically, affected patients have recurrent cold skin abscesses and chronic dermatitis (Fig. 1) and often develop sinopulmonary infections and pneumonia, frequently resulting in pneumatoceles. The infections mostly are bacterial and typically are caused by *Staphylococcus aureus*, although mucocutaneous candidiasis also may occur, as might secondary *Aspergillus* infections of pulmonary cavities from prior infections. A recent report of *Pneumocystis jiroveci* pneumonia in HIES patients also has been published. (3)

Patients usually have coarse facial features that include prominent brow and supraorbital ridge, with the impression of deep-set eyes, a wide alar base and broad nasal tip, thickened soft tissue of the ears, and pale, doughy skin (Fig. 2). Skeletal abnormalities include growth retardation, osteopenia, and decreased bone mineralization leading to fractures as well as dental abnormalities such as retained primary teeth. Dermatitis may be present in the first weeks after birth but typically is not present at birth.

HIES is characterized by markedly elevated serum IgE concentrations, ranging from 2,000.0 to 50,000.0 IU/mL. An elevated eosinophil count occurs often prior to acute infection. RAST testing can identify specific allergens that may be triggers, and a specific IgE blood test that measures allergen-specific IgE in human serum or plasma may be more sensitive and offers another alternative.

This syndrome is rare, with no reported incidence. The National Institutes of Health currently follow a large cohort of patients who have HIES; their goal is to provide more information about the incidence and development of HIES over time. Inheritance may follow an autosomal dominant or autosomal recessive pattern, although most cases seem to be inherited as an autosomal dominant trait with variable expressivity. The
underlying mutated gene responsible for HIES still is unknown, although defective neutrophil chemotaxis is exhibited in affected patients, which may contribute to the recurrent cold skin abscesses as well as recurrent pneumonias and chronic bacterial sinus infections.

Management
Management of HIES is difficult due to the lack of understanding of the pathophysiology of the immunodeficiency. The current goal is to manage the dermatitis similarly to atopic dermatitis and to prevent acute infections with follow-up and early diagnosis.

The management of dermatitis depends on its location, age of the patient, chronicity, and previous therapy. Treatment includes repairing and protecting the skin barrier with emollient creams and decreasing inflammation and pruritus with topical steroids and systemic antihistamines. Systemic steroids may be used for significant flares but are discouraged because of a rebound effect during weaning. Eliminating triggers such as foods, irritants, and other allergens must be addressed. Thus, allergy testing is recommended. Systemic antibiotics should be used for secondary bacterial skin infections, bacterial pneumonias, and sinusitis. Referral to an allergy specialist as well as a dermatologist should be considered when skin disease is recalcitrant. Other treatments have included cyclosporine, interferon-gamma, bone marrow transplant, and intravenous immune globulin. Because of the rarity of this syndrome, efficacy studies have been difficult to conduct on these treatments.

Lessons for the Clinician
HIES is a rare syndrome that should be included in the broader differential diagnosis of patients who have severe atopic dermatitis that does not improve with standard therapy. Due to the constellation of symptoms and clinical features associated with HIES, the history and physical examination along with serum immunoglobulin concentrations, including IgE, and differential eosinophil count should be used for evaluation. Parental education is of utmost importance, focusing on dermatologic management and expectations. (Caitlin M. Sgarlat, DO, Anne R. Sveen, MD, State University of New York, Upstate Medical University, Syracuse, NY)

References

Case 4 Discussion
The baby’s serum laboratory findings included: sodium, 162.0 mEq/L (162.0 mmol/L); potassium, 7.0 mEq/L (7.0 mmol/L); chloride, 128.0 mEq/L (128.0 mmol/L); bicarbonate, less than 5.0 mEq/L (5.0 mmol/L); BUN, 25.0 mg/dL (8.9 mmol/L); creatinine, 1.0 mg/dL (88.4 mcmol/L); and glucose, more than 600.0 mg/dL (33.3 mmol/L). An arterial blood gas showed a pH of 7.0 mEq/L (7.0 mmol/L); chloride, 128.0 mEq/L (128.0 mmol/L); bicarbonate, less than 5.0 mEq/L (5.0 mmol/L); BUN, 25.0 mg/dL (8.9 mmol/L); creatinine, 1.0 mg/dL (88.4 mcmol/L); and glucose, more than 600.0 mg/dL (33.3 mmol/L). An arterial blood gas showed a pH of 6.86, Pco₂ of 31.5 torr, Po₂ of 51 torr, and base excess −27.4 mEq/L. The boy was transferred immediately to the intensive care unit and started on an insulin drip for acute management of diabetic ketoacidosis (DKA).

Additional History
On additional questioning, it was discovered that type 1 diabetes mellitus had been diagnosed in the boy’s mother at age 8 months, in his grandmother at age 4 months, and in his half-brother at age 2.5 years. He also had an older sister who died at the age of 3 months. The parents were told that she most likely died from sudden infant death syndrome. They reported that the day prior to her death, she had experienced cold symptoms, including rapid breathing, and was evaluated in an ED and discharged from the hospital. Later that evening, she died in her sleep.

The boy’s past medical history revealed a birthweight of 3.49 kg (50th percentile). He was born by repeat cesarean section at 39 weeks’ gestation. His mother’s pregnancy was complicated by type 1 diabetes and a positive culture for group B Streptococcus. She took insulin throughout the pregnancy and smoked four to five cigarettes per day. Apgar scores were unknown, but the boy cried immediately following delivery and required no additional resuscitation.

Clinical Course
Following the boy’s stabilization, a head CT scan was obtained because of his lethargy; it revealed cerebral edema, ventricular hemorrhages, and cortical vein thrombosis. He was observed closely by the neurosurgeons but did not require surgical intervention. A septic evaluation had been initiated because of his fever, and all cultures were negative. His fever was determined to be caused by his viral upper respiratory tract infection.

With assistance from the endocrinology service, the boy was diagnosed as having diabetes type 1 and managed with an insulin pump. He now is a healthy 1-year-old and remains on an insulin pump, having a hemoglobin A₁C value of 7.1 g/dL.
The Condition
Type 1 diabetes is a disease characterized by immune-related destruction of insulin-producing pancreatic beta cells. Although most patients present in childhood, almost 25% are diagnosed as adults. There is some variation in the age of presentation for children, with peaks seen at age 4 to 6 years and again at age 10 to 14 years. Presentation as an infant is extremely rare but does occur. Studies performed in countries outside of the United States report an incidence of 1.4 to 1.96 cases of diabetes before the first birthday in a population of 100,000. The incidence of type 1 diabetes in all children varies among individuals of different ethnic backgrounds but is highest in whites.

Specific clues to the presence of diabetes in an infant include increased dietary intake, particularly of fluids; an increase in the number of wet diapers; and weight loss. The presence of these signs varies among individual patients.

Because gene polymorphisms are involved, family history plays a significant role in the epidemiology of type 1 diabetes. The incidence is increased in children of a mother or father who has been diagnosed as having the disease, and even more so if both parents have it. The incidence also is increased in siblings of affected individuals. Although many genetic factors are involved, most patients who have type 1 diabetes carry the human leukocyte antigen (HLA) DR3 or HLA DR4 haplotypes, with a heterozygote combination (DR3, DR4) placing an individual at the highest risk. When multiple family members are affected with type 1 diabetes, HLA typing can be helpful in estimating the risk of other relatives developing the disease.

Progression to DKA is seen exclusively in type 1 diabetes. Serious complications include fluid and electrolyte abnormalities, dehydration, and cerebral edema. Nearly 30% of deaths from DKA occur because of cerebral edema, which can be a complication of therapy. Timely treatment with carefully monitored fluid resuscitation and insulin therapy is essential.

Lessons for the Clinician
Consideration of a broad differential diagnosis for an infant who has tachypnea in the winter season is critical. This patient had typical signs of a viral upper respiratory tract infection, specifically, cough, congestion, and fever. However, these signs were mild, and his tachypnea was out of proportion to the extent of his viral illness. Copious nasal secretions, coarse breath sounds, retractions, and perhaps, the wheezing of bronchiolitis would be expected in an infant whose respiratory rate is as high as 80 breaths/min. In addition, his vital signs would be expected to improve following suctioning.

Distinguishing respiratory distress caused by a virus from the respiratory distress of deep, rapid (Kussmaul) respirations associated with DKA can be challenging, especially in a 2-month-old infant. Clues in this case that the underlying disorder was not primarily respiratory were present but perhaps not obvious; they included a drop in growth percentiles from the 50th percentile at birth to the 10th percentile on admission, a strong family history of early-onset juvenile diabetes, rapid deterioration of his clinical status, tachypnea without accompanying severe respiratory signs, and the family history of an infantile death of questionable cause in a sibling. In this child, the viral respiratory infection most likely precipitated the DKA.

Attention to details, thorough history-taking, and the consideration of a broad differential diagnosis even when the presentation seems basic are crucial in diagnosing disorders that can present in a misleading fashion but cause severe harm if undetected. (Lauri E. Blanch, MD, The Children’s Mercy Hospital, Kansas City, Mo.)

EDITOR’S NOTE. This case was selected for publication from the 10 finalists in the 2007 Clinical Case Presentation program for residents held by the Resident Section of the American Academy of Pediatrics. Dr Blanch was a resident when she wrote the case. Choosing which case to publish involved consideration of the teaching value and excellence of writing, but also the content needs of the journal. Another case will be chosen from the finalists presented at this year’s AAP National Conference and Exhibition and published in 2009.

—LFN

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