One Disease, Multiple Manifestations

Vani Selvan, MD; Tetyana L. Vasylyeva, MD; Curtis Turner, MD; and Osvaldo Regueira, MD

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CME EDUCATIONAL OBJECTIVES

1. Review the histopathology of Langerhan’s cell histiocytosis (LCH).
2. Discuss the varying clinical presentations of LCH.
3. Demonstrate currently recommended management strategies for the different presentations of LCH.

ABOUT THE AUTHOR

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Dr. Selvan, Dr. Vasylyeva, Dr. Regueira, and Dr. Turner have disclosed no relevant financial relationships.

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INSTRUCTIONS

1. Review the stated learning objectives of the CME articles and determine if these objectives match your individual learning needs.
2. Read the articles carefully. Do not neglect the tables and other illustrative materials, as they have been selected to enhance your knowledge and understanding.
3. The following quiz questions have been designed to provide a useful link between the CME articles in this issue and your everyday practice. Read each question, choose the correct answer, and record your answer on the CME REGISTRATION FORM at the end of the quiz. Retain a copy of your answers so that they can be compared with the correct answers should you choose to request them.
4. Type your full name and address and your date of birth in the space provided on the CME REGISTRATION FORM.
5. Complete the evaluation portion of the CME REGISTRATION FORM. Forms and quizzes cannot be processed if the evaluation portion is incomplete. The evaluation portion of the CME REGISTRATION FORM will be separated from the quiz upon receipt at PEDIATRIC ANNALS. Your evaluation of this activity will in no way affect the scoring of your quiz.
6. Your answers will be graded, and you will be advised whether you have passed or failed. Unanswered questions will be considered incorrect. A score of at least 80% is required to pass. Your certificate will be mailed to you at the mailing address provided. Upon receiving your grade, you may request quiz answers. Contact our customer service department at (856) 994-9400.
7. Be sure to complete the CME REGISTRATION FORM on or before February 28, 2009. After that date, the quiz will close. Any CME REGISTRATION FORM received after the date listed will not be processed.
8. This activity is to be completed and submitted online only.

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This CME activity is primarily targeted to pediatricians, osteopathic physicians, pediatric nurse practitioners, and others allied to the field. There are no specific background requirements for participants taking this activity. Learning objectives are found at the beginning of each CME article. This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Vindico Medical Education and PEDIATRIC ANNALS. Vindico Medical Education is accredited by the ACCME to provide continuing medical education for physicians. Vindico Medical Education designates this educational activity for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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EDUCATIONAL OBJECTIVES OVERVIEW

Early in each physician’s training, it is emphasized that every patient encounter offers an opportunity to be a detective. Using deductive reasoning based on the “clues” presented, the physician strives to solve the mystery of the patient’s illness. Dermatological issues most commonly present in the primary care setting and from there are referred to a specialist. As frontline evaluators of these complaints, each physician must, at times, play detective to discover the real cause for the patient’s symptoms.

This issue of Pediatric Annals presents three case vignettes in which the patient or patients suffer from an unusual systemic cause for their skin findings. As well, two short reviews of environmental causes for skin irritation are provided to alert the practicing healthcare professional to increasingly common but often overlooked chemical irritants in children.

After reviewing this issue of Pediatric Annals, the participant will be more keenly aware of subtle clues to systemic disease that present on a patient’s skin, as well as better able to provide counseling to families whose child has developed a sensitivity to chemical irritants.

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One Disease, Multiple Manifestations

Vani Selvan, MD; Tetyana L Vasylyeva, MD; Curtis Turner, MD; and Osvaldo Regueira, MD

CASE 1

A 5-year-old Hispanic girl was evaluated for recurrent torticollis over a period of 1 year, which was interfering with regular activities. Cervical spine studies were normal. Ibuprofen, rest, and parental reassurance were given. Two months later, she was evaluated for persistence of torticollis. On exam, she was apprehensive, her head was tilted to the left, and she refused to move her neck. The left posterior-lateral neck region was tender on palpation. The remaining physical and neurological exam was unremarkable. Magnetic resonance imaging (MRI) showed a destructive process of the left portion of the body of C2 extending into the left lamina and dens, not involving the spinal cord or vertebral artery (see Figure 1). An osteomyelitic process with an inflammatory phlegmon was considered. Biopsy revealed a histiocytic infiltrate with S100 and CD1a expression.

CASE 2

A 22-month-old male received oral antibiotics for an inflammatory process of the lower right hemi-mandible. A month later, the swelling persisted. A 3.5 x 10 x 1 cm ulcerative lesion destroying the right posterior alveolar ridge of mandible with a necrotic base and foul smelling discharge was noted. Within an anterior gingival tissue prominence, the upper portion of a tooth was seen protruding (see Figure 2, page 93). Several enlarged, non-tender firm lymph nodes measuring up to 1.5 cm were noted on the posterior triangle of the neck bilaterally. “Floating teeth” were seen by Panorex exam. Computerized tomography (CT) scan showed a destructive lesion in the body of the mandible. Biopsy revealed an infiltrate of histiocytes with S100 and CD1a expression.

CASE 3

A 14-month-old girl presented with bronchiolitis, anemia, hypoalbuminemia, mild thrombocytopenia, and hepatosplenomegaly. The week prior to admission, she had fevers up to 103°F with...
a clear nasal drainage and right inguinal lymphadenopathy. EBV titers were elevated. Minimal ascites and retroperitoneal adenopathy were noted by CT scan.

**CASE 4**

A 1-year-old boy presented with multiple scaly, maculoerythematous scalp lesions measuring up to 1 cm in diameter, which had been treated for a month as seborrheic dermatitis. He was appropriately developed for age, and no other abnormal findings were present on physical and radiological exam. Biopsy revealed S100 and CD1a positive histiocytic infiltrate (see Figure 4, page 94).

**DISCUSSION**

Langerhan’s cell histiocytosis (LCH) consists of a group of syndromes characterized by an abnormal increase in the number of dendritic antigen presenting cells involving single or multiple organs.** Although the etiology and**

*Although the etiology and pathogenesis of LCH are still unknown, it is suggested it may be a reactive disease caused by abnormal immune regulation.*
The clinical manifestations of LCH depend on the site of the lesions and organs and systems involved. Single-system or unifocal LCH presents with solitary or few indolent and chronic lesions of bone or other organs. Multi-system or multifocal LCH can present as an acute, fulminant, disseminated disease (Letterer-Siwe disease). The clinical triad of multifocal bone lesions, diabetes insipidus (DI), and proptosis (Hand-Schüller-Christian disease) is rarely noted. The LCH infiltrate may involve bones, skin, teeth, gingival tissues, ears, endocrine organs, lungs, liver, spleen, lymph nodes, and bone marrow, interfering with normal function. In the initial evaluation, a skeletal survey will show bone involvement in 78% of cases. Lesions may affect the skull (49%), pelvic bone (23%), femur (17%), orbit (11%), and ribs (8%).

Spinal involvement may be asymptomatic or painful and can present as torticollis or back pain. The thoracic vertebrae are most commonly involved, followed by the cervical and lumbar. Verterbral body collapse (“vertebra plana”) and neurological deficits may occur. Mastoid process involvement can mimic mastoiditis, while that of the ossicles may result in deafness. Gingival and soft tissue swelling, fractures, or pain characterize mandibular involvement with “floating teeth” noted in a Panorex exam. Orbital involvement may cause proptosis. Unfavorable prognostic factors include age of < 2 years, the presence of anemia, liver and spleen involvement, and respiratory failure. Bone marrow dysfunction in LCH is associated with hepatosplenomegaly and pancytopenia and has a very poor prognosis. An affinity for bile duct involvement can lead to sclerosing cholangitis and, eventually, biliary cirrhosis.

DIAGNOSIS

Technetium MDP bone scan is useful for evaluation of age and activity of lesions. Still, lesions are not visualized by these techniques in 16% to 19% (by scan) to 29% (by plain film) of cases. Positron emission tomography (PET)-CT imaging has detected lesions missed by these methods. Patients with multiple lesions are at an increased risk of recurrence (18%) but especially so if skull lesions are present (39%). Cutaneous lesions need assessment of systemic involvement and skin biopsy are needed to differentiate it from common dermatological disorders. A definitive diagnosis is made by the typical histological features of Langerhan’s cells and immunophenotype with expression of S-100, CD1a, and langerin (CD207). Electronic microscopy is now seldom required to identify Bierbeck granules.

TREATMENT

Treatment varies depending on extent of involvement. Curettage, intralesional steroids, or radiotherapy may suffice for solitary bone lesions. Patients with multiple system involvement are considered “high risk” if the liver, spleen, lungs, or hematopoietic system are involved. Prednisone, vinblastin, and intermediate dose IV methotrexate are given initially. 6-MP, prednisone, vinblastine, and oral methotrexate may then follow for up to a year. Patients with multiple system involvement in the “low-risk” category...
may receive similar initial therapy with prednisone and vinblastine administered during continuation therapy for up to a year. Guidelines for therapy are delineated in the LCH-III protocol, to which the reader is directed as an invaluable reference. Novel agents such as 2-CDa with high dose Ara-C, tumor necrosis factor inhibitor, and pamidroate have been tried with varying success. Treatment of vertebral lesions by Brown et al included external support of the involved vertebra initially by bracing followed by thoracolumbar sacral orthosis, soft tissue collar, or Jewett brace for a variable time period depending on clinical evolution. Surgery, steroids, chemotherapy, and radiotherapy were also utilized in some patients.

Dermal lesions may benefit from local or systemic steroids. Topical tacrolimus, 20% nitrogen mustard, and psoralens with ultraviolet radiation have been tried with limited success. Endocrine evaluation is strongly encouraged for patients with polyuria (DI) and may be controlled with intranasal DDAVP spray applications.

All four of our patients responded to treatment with resolution of their lesions, normalization of blood counts, and overall clinical improvement. Our patient with skin involvement required additional treatments, including topical tacrolimus, topical nitrogen mustard applications, oral thalidomide, and oral methotrexate.

CONCLUSIONS
Although rare, LCH can present the pediatrician with a challenging diagnostic and treatment dilemma, mimicking various disease processes. Clinical findings can be insidious or overt and may range from a single isolated skin lesion to varying involvement and functional compromise of multiple organ systems. Early diagnosis, treatment, and long-term follow-up care by a multidisciplinary team are critical for the long-term prognosis.

REFERENCES