

Refinement of Radiation Therapy Based on PET Data in an Adult With Langerhans Cell Histiocytosis of Soft Tissues

Stephanie E. Weiss, MD¹
Lynn O'Connor, MD, MPH¹
James S. Welsh, MD²

¹ *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Baltimore, Md*
² *University of Wisconsin
Madison, Wis*

Formerly known as histiocytosis X, Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder of activated Langerhans cells with a variety of clinical presentations.¹⁻³ Treatment options depend upon the particular clinical presentation and are based on disease extent, rapidity of progression, and specific sites involved. Localized disease can be effectively controlled with low-dose radiation therapy.^{4,5} LCH is often considered a pediatric disorder but adults are occasionally affected,^{6,7} and in such cases the disease is typically limited to a single bony site. We report a rare case of soft-tissue LCH in an adult whose planned course of radiation therapy was modified based on 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) findings.

Case Report

A 42-year-old woman from Saudi Arabia noted a firm, freely movable, and painless swelling in the left supraclavicular region. The mass increased in size and became tender and the patient sought medical attention 8 months later. Multiple biopsies performed in Saudi Arabia revealed both acute and chronic inflammatory changes but no specific pathologic etiology. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed only a large supraclavicular mass and an irregularity of the true vocal cords prompting an otolaryngology consult. Biopsy of the cords via upper endoscopy revealed only actinomycosis, which responded to penicillin. The left supraclavicular mass remained, however, and became progressively more painful. Local symptoms progressed to include swelling, weakness, and decreased sensation in the left upper extremity. Repeat CT showed subclavian vessel compression and tracheal displacement. The mass appeared to involve the left paraspinal muscles.

At this time the patient was transferred to our institution for further management and open biopsy, which revealed a mixed inflammatory infiltrate of eosinophils, histiocytes, and lymphocytes in a fibrotic background that completely obliterated normal lymph node architecture. Polarizable material with a foreign body giant cell reaction was noted. Immunohistochemistry was positive for CD1a and S-100 protein. Final pathologic diagnosis was LCH. There was a delay between the patient's medical oncology consultation and her referral to radiation oncology because visa issues required she return to her home country. Upon her return to consult in our department, examination revealed a 10 × 5 × 4-cm firm, immobile, erythematous, nontender mass. Strength in the left upper extremity was diminished and there was decreased sensation in the left C5 to T1 dermatomes. The diagnostic CT images were lost in transit from Saudi Arabia and only faxed reports were available for our review. At this time the patient refused repeat diagnostic CT imaging but did agree to PET imaging in order to evaluate the extent of involvement. This scan revealed focal intense abnormal FDG accumulation in the left supraclavicular region extending into the left neck, corresponding to the prior CT report. An additional focal area of abnormal tracer accumulation was seen in the left anterior/superior mediastinum. Based on these findings, we recommended CT-based radiotherapy treatment planning rather than the initially scheduled fluoroscopic simulation.

Images obtained by CT simulation confirmed the presence of a 10-cm mass in the supraclavicular region and demonstrated a 3-cm left anterior mediastinal mass consistent with the area of increased uptake on PET imaging. The patient was treated with dexamethasone for acute relief of symptoms, and definitive radiation to a dose of 15 Gy (in 2.5-Gy fractions) to the left supraclavicular region and mediastinum. She then received another 12 Gy (in 2-Gy fractions) to the supraclavicular site for a total dose of 27 Gy to the supraclavicular mass and 15 Gy to the mediastinum.

Address correspondence to:
James S. Welsh, MD, Medical Director, UW Cancer Center/Riverview, |
Wisconsin Rapids, WI 54494; Tel: 715-421-7442; Fax: 715-421-7408;
E-mail: welsh@humonc.wisc.edu.

By the conclusion of radiation therapy, the patient reported relief from left arm pain and numbness, and improved strength. Initial 4-month follow-up CT scan revealed a substantial decrease in the size of the supraclavicular mass from 10 cm to 4 cm and complete resolution of the mediastinal mass. At 8 months posttreatment, the primary mass had completely disappeared on examination. Repeat PET imaging revealed no residual activity at the treated sites and no new sites of activity. The patient reported that all symptoms had fully resolved. She has remained clinically and radiographically free of disease by CT imaging at 31 months' follow-up.

Discussion

In 1953 Lichtenstein⁸ introduced the term "histiocytosis X" to describe a group of conditions with variable clinical presentations but shared histologic features. The disease is now known as Langerhans cell histiocytosis secondary to the characteristic proliferation of pathological Langerhans cells. LCH is a neoplastic^{9,10} disorder of activated Langerhans cells, which are bone marrow-derived antigen-presenting cells.¹¹ These cells express CD1a and S-100 protein, and they are characterized by the ultrastructural presence of Birbeck granules in the cytoplasm. Other cell types found in LCH lesions include lymphocytes, macrophages, eosinophils, and multinucleated giant cells. When the clinical presentation is limited to one site, as is typically seen in children and young adults, it is characterized as eosinophilic granuloma of bone. Another variant, Hand-Schüller-Christian disease, typically consists of multifocal bone lesions and associated lesions in lymph nodes, skin, and abdominal viscera. This pattern is most common in children under 5 years of age. Younger children (typically under 2 years of age) may present with more widespread disease, with lesions involving bone, skin, marrow, lymph nodes, liver, spleen, lungs, gastrointestinal tract, endocrine glands, and the central nervous system. This disseminated form, Letterer-Siwe disease, has a relatively poor prognosis. Treatment paradigm and ultimate prognosis are highly dependent upon extent of dissemination, so it is critical that patients receive a thorough radiologic work-up to distinguish isolated lesions from more widespread or disseminated disease.

A skeletal survey can reveal osteolytic bony involvement, which has characteristic appearances at specific locations.¹¹ Technetium Tc-99m bone scintigraphy may reveal uptake of radiotracer by blastic tumors; however, the false-negative rate is as high as 35%,¹²⁻¹⁴ most likely because of the high rate of lytic lesions. Magnetic resonance imaging (MRI) may demonstrate areas of marrow replacement on T1 images and increased signal on T2 images. Soft tissue involvement may be detected on CT

and MRI.^{12,15,16} The use of indium 111 pentetretotide scintigraphy in patients with LCH has been reported.¹⁷

Our patient presented with several unusual features. First, the diagnosis of LCH in a middle-aged woman is highly unusual. LCH is primarily a disorder of children and young adults. Secondly, adults diagnosed with LCH typically have isolated bone or skin involvement as the most frequent presentation. Our patient presented with a soft tissue mass that did not appear to arise from adjacent bone.

For localized disease, low-dose involved-field radiotherapy provides excellent control⁵ and was considered the treatment of choice for our patient. Because of the low doses required and the tendency for localized disease to be limited to bone, radiation treatment planning typically is simple and CT simulation is not mandatory. However, when the disease involves soft tissue, CT treatment planning may be helpful in defining the true extent of disease and assuring adequate coverage by the radiotherapy fields. Because this patient refused a second diagnostic CT after the loss of her initial films, a PET scan was obtained. The PET scan elucidated an unexpected site of mediastinal soft tissue disease, which prompted us to switch to CT-based planning and change our treatment portal.

There are few reports on the use of PET in LCH. Calming and colleagues¹⁸ showed PET scan alterations in patients with known LCH of the central nervous system. The PET scans revealed areas of altered metabolism and function in 6 of the 7 patients studied, suggesting a possible role in monitoring the disease over time. Blum and coauthors¹⁹ reported two cases where this modality was positive and facilitated therapeutic monitoring. In our case, the PET information led to an alteration of management in terms of radiation treatment planning and ports. Instead of the fluoroscopic simulation, which would have missed the mediastinal mass, the patient underwent CT simulation, confirming and allowing targeting of the previously unidentified disease. Although the initial diagnostic CT scans reported no abnormalities in the mediastinum, PET data elucidated a clearly visible abnormality on the radiotherapy treatment-planning CT. The radiotherapy fields were tailored to accommodate the additional areas of involvement and the radiation doses prescribed reflected the relative volume of disease. Based on our case, we would suggest PET or PET/CT in cases in which tumor volume is equivocal and definitive radiotherapy is planned.

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Review

Robert J. Arceci, MD, PhD

Director and King Fahd Professor of Pediatric Oncology

Professor of Pediatrics and Oncology

Sidney Kimmel Comprehensive Cancer Center

at Johns Hopkins University

Baltimore, Md

The histiocytoses are a diverse group of disorders that result from excessive and uncontrolled proliferation of cells of the mononuclear phagocytic system. They have varied clinical presentations and outcomes. Although their relatively low incidence has precluded extensive investigations, more recent international cooperation has

helped to further both our understanding and our ability to treat patients effectively.

The term "histiocyte" is derived from "histio" meaning tissue and "cyte" meaning cell. Histiocytes were therefore simply described as cells found within various tissues, a rather nondescript and not particularly helpful term. "Histiocytosis" thus came to be used to describe all disorders in which increased numbers of histiocytes were found. The world of biological investigation into the lineage derivation and function of histiocytes and that of the clinical description of the histiocytic disorders progressed in parallel over the course of a century before beginning to merge their observations into our current understanding of these enigmatic disorders.

With the description of macrophages in starfish larvae by Metchnikov and the first description in the 1800s of dendritic cells by Paul Langerhans, then a medical student, the initial bricks were placed in the foundation of what would be termed the reticuloendothelial system (RES) by Aschoff. "Reticulo" was used to refer to the lattice or reticulum formed by cytoplasmic extensions of these cells, and "endothelial" refers to the cells' characteristic proximity to vascular endothelial cells. Subsequently, van Furth introduced the term mononuclear phagocytic system, based on his belief that this better described the morphologic and functional characteristics of the RES.^{1,2}

During this period of biological investigation, the first clinical descriptions of patients with various forms of histiocytosis were published. In 1893, Hand published a description of a 3-year-old boy presenting with failure to thrive, exophthalmos, hepatosplenomegaly, lymphadenopathy, rash, diabetes insipidus, and lytic skull lesions.³ In 1915, Schüller reported 3 patients with skull lesions, some of which were self-resolving.⁴ Four years later, Christian reported a patient with skull lesions, exophthalmos, and diabetes insipidus, as well as oral ulcerations leading to floating or loose teeth.⁵ When combined, these initial descriptions led to the eponym Hand-Schüller-Christian disease. In 1924, Letterer described a 6-month-old infant with cough, tachypnea, rash, hepatosplenomegaly, and cytopenias.⁶ Nearly 10 years later, Siwe described a 16-month-old girl with fever, rash, lymphadenopathy, lytic bone lesions, hepatosplenomegaly, and cytopenias.⁷ Both of these patients died from progressive disease, which was felt to be due to the proliferation and organ infiltration of large cells derived from the RES. The eponym Letterer-Siwe disease was coined to describe this fulminant form of histiocytosis. Eosinophilic granuloma has been used to describe bone lesions based on their characteristic pathology showing a mixed cellular infiltrate. Dr. Sidney Farber unified these different historic eponyms by stressing that they all shared a similar pathology.⁸ Subsequently, Lichtenstein proposed that they all be termed "histiocytosis

Address correspondence to:

Robert J. Arceci, MD, PhD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, The Harry and Jeanette Weinberg Building, Suite 1100, 401 North Broadway, Baltimore, MD 21231; E-mail: arceco@jhmu.edu.

X," based on the presence of the X body—later termed the Birbeck granule—in the predominant lesional cells.⁹ At approximately the time Lichtenstein proposed the term histiocytosis X, Farquhar and Clairveaux described an infant with a familial and rapidly fatal form of a disorder that resembled Letterer-Siwe disease but was characterized by profound hemophagocytosis.¹⁰ A subsequent report by Nelson¹¹ of a similar case, but one characterized by extensive central nervous system involvement, led MacMahon to classify this distinct group of disorders as familial erythrophagocytic lymphohistiocytosis.¹²

The critical studies of Nezelof and colleagues were the first to link the Langerhans cell to those disorders referred to as histiocytosis X, thus leading to the term Langerhans cell histiocytosis (LCH), while the hemophagocytic syndromes remained distinct and primarily considered disorders of proliferating lymphocytes and macrophages.¹³ In 1987 the Histiocyte Society developed the first comprehensive classification system of these disorders based on both pathobiology and clinical findings.¹⁴ This system delineated the histiocytoses into Class I, which included primarily the LCHs, Class II which included primarily the inherited and secondary hemophagocytic lymphohistiocytoses, and Class III, which included malignant disorders of the mononuclear phagocytic system.¹⁴ Although more recent refinements of this classification system have arisen to include other disorders such as juvenile xanthogranulomatous disease and Erdheim-Chester disease (considered part of the dendritic lineage) and Rosai-Dorfman disease (considered a reactive macrophage disorder), the basic distinction between dendritic and macrophage proliferative disorders has been maintained.^{2,15}

The etiology of LCH remains unknown. However, the high concordance in identical twins, aberrant morphology, biochemical expression patterns, and maturation status of lesional Langerhans cells, along with the demonstrated clonality and chromosomal changes observed in lesional Langerhans cells, have led to the conclusion that LCH represents a group of clonal, proliferative disorders of immature Langerhans cells with variable clinical manifestations.^{1,16} The hemophagocytic lymphohistiocytoses have now been shown to result in the familial forms from inherited gene mutations regulating the effective expression of cytolytic T-lymphocyte granules, such as perforin.¹⁷⁻¹⁹

A critical realization over the past two decades has been an increased appreciation that these disorders, once believed to only afflict children, also occur in adults of any age.²⁰⁻²³ In addition, the belief that adults primarily develop isolated bone disease has also been dispelled. Arico and colleagues reported from survey results that nearly 70% of adult patients with LCH have multisystem disease with approximately 30% having diabetes insipidus.²³ Only 31% had single-system disease with about

half of them displaying isolated pulmonary involvement.²³ There is currently an open international trial sponsored by the Histiocyte Society for adults with LCH, including isolated pulmonary involvement. This trial is being performed to determine the effectiveness of vinblastine and prednisone in adult patients with multisystem disease as well as assessing patients with isolated pulmonary disease following smoking cessation or with a trial of steroids for those with progressive lung involvement.²⁴

The work-up of patients with LCH is another important aspect of the assessment and risk stratification of patients in order to direct therapy. A carefully taken history and physical examination are essential. Further work-up usually involves a skeletal survey and technetium-based bone scan. Depending upon suspected clinical involvement, patients may also benefit from CT scanning of the chest, abdomen, and pelvis. The recognition of central nervous system involvement has led many histiocytosis experts to recommend a brain MRI with gadolinium contrast at the time of diagnosis. Complete blood counts and liver function tests should also be done. The erythrocyte sedimentation rate or C-reactive protein, markers of inflammation, may also be helpful in following disease activity and response to therapy. Further tests such as pulmonary function tests, lung or liver biopsy, or endocrinological evaluation should be done if clinically indicated.

In the context of the above discussion, the clinical case study by Weiss, O'Connor, and Welsh²⁵ raises several important issues. The first is that of proper staging of both children and adults with LCH. Although the role of PET scanning may prove useful in LCH, there are currently insufficient data to provide evidence for this. The role of PET scanning is clearly an area of investigation that requires further study. A future approach will hopefully be to use radiolabeled monoclonal antibodies, such as against the Langerhans cell marker CD1a, to perform diagnostic and staging evaluations as well as to potentially treat patients.²⁶ A second issue is that adults with LCH commonly present with multisystem disease—including skin, skeletal, lung, liver, CNS, and lymph node involvement—not with just single-site disease. A third issue is treatment. Most adults will respond to treatments similar to those used in children, although careful dose adjustments are often necessary to effectively manage adverse drug-related toxicities, especially peripheral neuropathy, which can be associated with vinblastine. In children, the use of radiation therapy has become relatively rare, based on concerns of secondary malignancies, even with low-dose therapy, and the significant incidence of recurrent disease, especially in those patients with multisystem disease. Thus, patients with multisystem or extensive single-system disease will usually benefit from the use of

systemic therapy. A similar situation is likely to manifest in adults with LCH, although prospective trials need to be conducted to legitimize such a recommendation.

Lastly, LCH in adults, as in children, is often a significant disease that can be associated with considerable morbidity and mortality in patients with extensive or isolated pulmonary disease. LCH should be managed in adults with multidisciplinary approaches as used in both children and adults with cancer. It is only through cooperative group prospective clinical trials that anecdotal observations will give way to definitive recommendations regarding therapy and long-term assessments for adults. Far better to learn from the history of the pediatric experience than to be doomed to repeat it for adults with LCH.

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