CASE REPORT

Adult Langerhans cell histiocytosis: An unusual cause of referred knee pain

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Abstract

Langerhans cell histiocytosis (LCH) in adults is rare and regarded as an 'orphan disease.' The systemic symptoms of LCH can mimic many other undifferentiated diseases seen at the primary care level. Failure to diagnose and delays in referral are common pitfalls in the management of this disease. We present a case of a 34-year-old woman with referred knee pain who was eventually diagnosed with multi-system LCH 4 years after the initial presentation. The mean age of presentation of LCH symptoms in adults is 33. Bone lesions are the frequent presentation of LCH in this age group. Endocrine involvement in LCH is seen in the form of diabetes insipidus (DI), which remains the most common extraskeletal presentation of LCH in adults. In the case discussed here, a definitive diagnosis of LCH was established through tissue biopsy. The spectrum of undifferentiated symptoms underscores the difficulty and delay in making a diagnosis associated with the condition. Most GPs not only face the predicament of initial recognition but also fail to merge presenting symptoms to form a purposeful referral of this elusive disease to a tertiary care unit.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease caused by the clonal proliferation of abnormal Langerhans cells in the bone marrow.[1] These cells comprise atypical myeloid dendritic cells, lymphocytes, macrophages, eosinophils and neutrophils.[1] The accumulation of these cells in the body causes osteolytic bone lesions, endocrine disorders, skins rashes, lymphadenopathy, splenomegaly and dysfunctions of the lung, liver and bone marrow.[1]

LCH can affect any age group.[2] However, the literature on LCH appears to indicate that two- thirds of the cases are diagnosed in childhood.[2] The onset of disease can occur at any age in adults, although the median age for the presentation of the disease is 30.[1] Patients with the 'single-system' disease, i.e., localized to one organ system , are usually males and have a good prognosis with minimal or even no treatment.[1,2] However, patients with a 'multi-system' manifestation face a poor outcome with a 10 – 20% chance of mortality and a 50% chance of life- impairing morbidity.[2]

Case Report

A 34-year-old lady presented to her GP with intractable bilateral knee pain ofmore than 1 month in duration. According to the patient, the pain had appeared to emanate from both sides of her hip for 3 years. At the time of presentation, the knee pain was much more accentuated and worse on the left side of the joint. Previously, she had experienced multiple recurrences occurring at progressively shorter intervals. During these flare ups, she walkedwith an antalgic gait, especially when the pain became unbearable. She also noticed that she also experienced pain over the hip whenever she walked for a prolonged period of time. The hip pain almost always followed an unusual, dull, aching pain over both knees. The pain was alleviated upon rest. The hip joint did not reveal any physical findings upon examination. However, the patient exhibited a slight, fixed flexion deformity of the right knee and hip joint. Up until this point, she had been relying on Mefenamic acid and Paracetamol, as required. She also took Celebrex occasionally when the pain became intolerable. She was compelled to stop working as an accountant approximately 3 years prior to presentation, as long-distance driving made both hip and joint pain worse.

2 years ago, she developed a sudden bout of polydipsia and polyuria which lasted for 3 months. She developed a preference for

cold water and began consuming it in large amounts. She visited her GP once again, who then ran several blood tests in an attempt to identify the cause of her complaint. After blood tests revealed persistently high sodium levels, she was referred to an endocrinologist for further work up. She underwent a water deprivation test, followed by a vasopressin challenge test, which confirmed the diagnosis of central diabetes insipidus (DI). A magnetic resonance imaging of the brain revealed an infiltrative lesion at the posterior aspect of the pituitary gland measuring 5.0mm x 5.0mm x 4.0mm. She was advised to use intranasal desmopressin on a daily basis. Her symptoms gradually subsided over a span of a week. She still has scheduled appointments at the tertiary care endocrine clinic to monitor the effectiveness of treatment, symptoms indicative of recurrence and her serum sodium levels. To date, she has no polyuria, increased thirst or recurrent headaches.

A decision was made by the GP to order an x-ray series of chest, lumbosacral, hip, pelvic and knee radiographies. Interestingly, the hip x-ray revealed multiple lytic lesions extending from the intertrochanteric to the proximal femur of both femurs (**Figure 1**). The cortex of the bone appeared thickened, but there was no evidence of cortical destruction. All other x-ray films were found to be normal. At this juncture, the GP suspected multiple myeloma (MM), extra-pulmonary tuberculosis (EPTB) or LCH.

The GP subsequently performed several other non-radiological tests to ascertain the diagnosis. The results of the blood investigations (**Table 1**) did not reveal anemia, elevated serum protein levels or unexplained renal or liver dysfunction. Tumor marker levels, including CA125, CA19-9, CEA and α fetoprotein, were not significant. However, both the erythrocyte sedimentation rate (ESR) and C-reactive (CRP) levels were elevated. The possibility of extra-pulmonary tuberculosis was ruled out with an induration of 10mm from the tuberculin sensitivity test (TST) after 72 hours. Also, a low A/G ratio lessened the suspicion of MM in this case.

An urgent referral was made to an orthopedician, and she underwent a bone biopsy procedure a week later. The biopsy revealed histiocytes that were reactive to CD1a and S100 stains. A definitive diagnosis of multi-system LCH(with the involvement of the intertrochanteric region of the bilateral femurand posterior pituitary gland) was made. The patient was referred to an oncologist to decide on further treatment options.

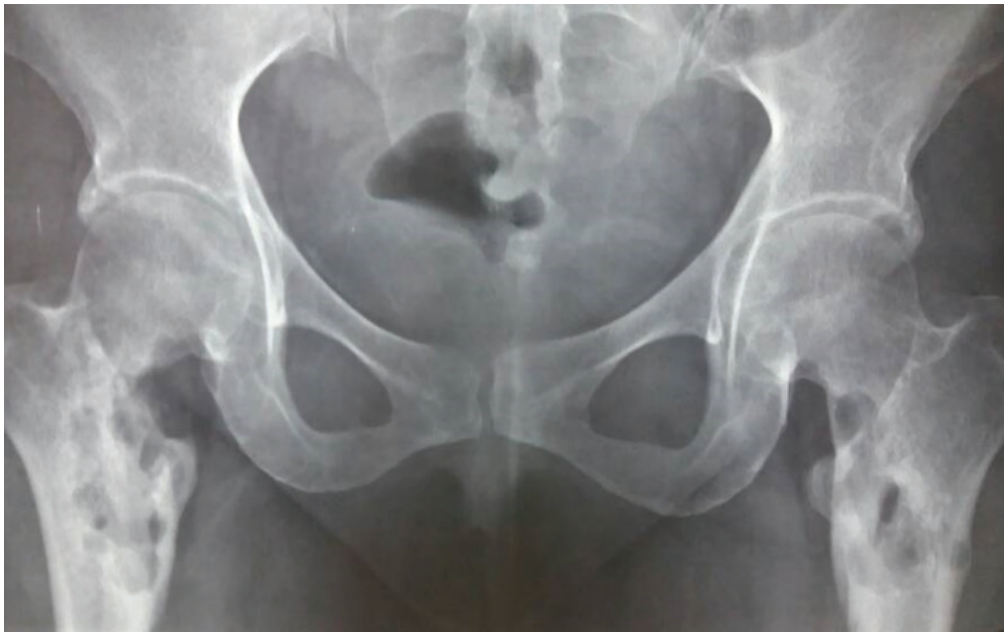

Figure 1: Multiple lytic lesions extending from the intertronchanteric to the proximal femur of both femurs

Table 1: Results of theblood investigations of the patient done at the primary care clinic

Test	Result	Unit	Reference Range
Full Blood Count			
Total white cell blood count	11.1	109/L	4.0-11.0
Total red blood cell	4.98	1012/L	4.5-6.5
Hemoglobin	13.5	g/dL	13.0-18.0
Packet cell volume	41.3	%	40-54
Mean corpuscular volume	82.9	fL	76-96
Mean corpuscular hemoglobin	27.1	PG	27-32
Mean corpuscular hemoglobin concentration	32.7	g/dl	30.0-35.0
Red cell distribution width	13.0	%	11.6-15
Platelets	343	109/L	150-400
Neutrophil	57.4	%	40-75
Lymphocyte	31.6	%	20-45
Monocytes	7.8	%	2-10
Eosinophils	2.8	%	1.0-6.0
Basophils	0.4	%	1
Erythrocyte sedimentation rate	77.0	mm/hr	4-14
C- reactive protein	16.5	mg/L	0-5
Renal Profile			
Urea	2.6	mmol/L	3.6-8.5
Sodium	137	mmol/L	132-152
Potassium	3.4	mmol/L	3.5-5.1
Chloride	99.1	mmol/L	96-108
Creatinine	66	mmol/L	60-130
Calcium	2.15	mmol/L	2.12-2.52
Corrected calcium	2.20	mmol/L	
Phosphate	1.11	mmol/L	0.81-1.58
Liver Function Test			
Total protein	76	g/L	60-85
Globulin	40	g/L	25-39
Albumin	36	g/L	34-50
AG ratio	0.9		0.9-1.8
Alkaline phosphate	98	U/L	50-136
Aspartate transaminase	45	U/L	15-37
Alanine transaminase	58	U/L	30-65
CA 125	9.4	U/mL	<35
CA 19-9	2.2	U/ml	<37
CEA	1.0	ng/ml	<5
α fetoprotein	5.2	ng/ml	<6.7

Discussion

LCH affects mainly children and occurs in only 1 – 2 per million adults.[3] According to the report of the International Registry of the Histiocyte Society (IRHSA) on adult LCH, the mean age of first manifestation in adults was 33 years, with a peak between 20 to 30 years.[4] This finding coincides with the initial presentation of symptoms related to LCH in our patient at the age of 31. There are no environmental risk factors associated with LCH, with the exception of cigarette smoking.[3,4] There is either no gender predominance or a slight predominance of female adult LCH patients.[5]

'Single-system' disease is found in 31.4% of patients, while 68.6% have the 'multi-system' form of the disease.[4] Skeletal involvement is one of the most common features of LCH in adults,[5,6] and osseous lesions are seen in 60% of adults.[7] LCH can occur in any bone in the body, but it is seen frequently in the skull, followed by the proximal femur and ribs.[1,7] The majority of patients have well-localized bony pain as the main presenting symptom.[7] A large proportion of skeletal lesions can remain asymptomatic but can also present as a painful swelling.[6] The classical appearance of bone lesions in LCH remain mostly lytic, although osteoblastic lesions occur occasionally.[6] LCH lesions appear as well-defined osteolytic areas with or without periosteal reaction and may resemble' malignancies.[6] The detection of skeletal LCH is based on a tissue biopsy. Electronic microscopic evaluation of the tissue biopsy will reveal Birbeck granules, whereas immunohistochemistry testing will exhibit positivity for the S100 protein and CD1a antigen.[6,8]

Posterior pituitary dysfunction in LCH patients is seen in the form of DI.[1] DI remains the second most common form of extra-skeletal involvement in LCH.[9] DI is also a frequent endocrine anomaly in adult LCH, with a prevalence rate ranging between 5 and 50%.[4,6,8] DI can occur either early or late in the course of the disease and represents the most common sign of central nervous system involvement.[1] As with our patient, DI can be the presenting feature predating the diagnosis of LCH, but it usually develops within a year following the initial diagnosis of LCH.[6] However, it can occur at any time during the course of the disease.[6] A full 51% of patients presenting with DI will develop other LCH manifestations within the following year.[6] DI is a permanent consequence of LCH seen in 24 – 40% of adults.[6] Pituitary MRI findings include pituitary stalk enlargement with loss of the posterior pituitary bright spot.[8]

LCH can often masquerade as other diseases due to a significant overlap in systemic symptoms. Besides skeletal and endocrine involvement, as in this case study, LCH can also present with lesions of the skin and lungs among a high proportion of adult patients. Seborrheic dermatitis has been reported to be a common lesion of the skin.[5] Whereas, infiltration of the lungs with LCH may produce a dry and unproductive cough with dyspnea.[5] Patients may also present acutely with acute dyspnea in the form of pneumothoraces, chest pain, fever, hemoptysis and weight loss. Therefore, LCH can present with obscure and undifferentiated symptoms which could lead to difficulty in establishing a prompt diagnosis.

This case demonstrates the importance of detailed history taking, a high index of suspicion and urgent referral in a primary care setting. Although the exact diagnosis was initially overlooked, a targeted assessment by the GP helped steer the management of this case in the right direction. Furthermore, swift cross consultations between specialists at the tertiary care unit and the GP expedited the discovery of this rare case in an adult patient.

Conclusion

This case report describes an individual with a step-wise progression of a 'multi-system' manifestation of LCH in an adult ina primary care setting. The sequence of the symptoms initially commenced with: 1) bony pain over the hips, 2) symptoms of DI and 3) referred pain to the knees. The spectrum of undifferentiated symptoms underscores the difficulty and delay in making a diagnosis associated with the condition. However, as evidenced by this case study, GPs can overcome this conundrum by: 1) guiding the referral of the patient and 2) initiating crucial communication with tertiary centers. Adopting these steps helped expedite the diagnosis and ultimately the treatment of this disease in our patient.

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Competing Interests

The authors report no conflicts of interest. The authors alone were responsible for the content and writing of the paper.

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How does this paper make a difference to general practice?

- This case report describes the process taken by GPs in the discovery of an elusive 'multi system' manifestation of LCH in an individual who presented initially with a common complaint of knee pain ina primary care setting.
- The spectrum of undifferentiated symptoms underscores the difficulty and delay in making adiagnosis associated with the condition.
- Delayed recognition of the disease can be prevented by having a high index of suspicion regarding patients presenting with unusual systemic symptoms and also by forging meaningful collaborative working relationships with tertiary healthcare providers in order to expedite purposeful referral of this elusive disease.

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