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【 CASE REPORT 】

A Case of Spontaneous Regression of Adult Multi-system Langerhans Cell Histiocytosis Presenting as Liver Tumor Rupture

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Abstract:
Adult multisystem Langerhans cell histiocytosis (MS-LCH) is rare and has a poor prognosis. A 67-year-old man with MS-LCH presented with a hepatic tumor rupture and multiple masses in the lungs, liver, and pancreas. Despite the initial aggressive disease course and involvement of organs at risk, the patient experienced spontaneous regression and lesion disappearance following smoking cessation without chemotherapy. A literature review revealed a distinct subset of MS-LCH that can be managed by smoking cessation and careful observation through follow-up imaging. This suggests that careful observation through follow-up imaging may be a reasonable alternative to chemotherapy in select adult cases of MS-LCH.

Key words: multi-system Langerhans cell histiocytosis, rupture of liver tumor, smoking cessation, spontaneous regression

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by proliferation and dissemination of CD1a and Langerin (CD207)-positive Langerhan-like cells in various organs (1). The incidence of LCH is low, estimated at 3-9 individuals per million, and is even rarer in adults, affecting 1-2 individuals per million (2).

Genetic investigations have revealed the presence of the *BRAF V600E* mutation in over half of the LCH cases (3). In cases of wild-type *BRAF*, genes involved in the MAPK pathway, such as *MAP2K1*, *MAP3K1,* and *ARAF*, may harbor mutations, resulting in consistent activation of the MAPK pathway (1, 4). Clinical manifestations of LCH vary depending on the organ involved. LCH predominantly affects the skin and bones and may manifest as refractory dermatitis or bone pain (5, 6). However, LCH can infiltrate any organ; therefore, it can be classified into four types based on the number of lesions and the type of organ involved: unifocal, single-system multifocal, single-system pulmonary, and multi-system LCH (MS-LCH) (6).

In adults, the prognosis is contingent on the type of LCH, but the 5-year survival rate is generally favorable (approximately 90%) (7-9). However, in cases of MS-LCH involving organs at risk, such as the liver, spleen, and bone marrow, the overall survival drops to almost 50%-60% (7). The international expert consensus recommends initiating chemotherapy, including vinca alkaloid / steroid-based and antimetabolite-based regimens, for patients with MS-LCH who have impending organ damage or symptoms, while watchful waiting and careful surveillance can be a treatment option before symptoms or organ damage develop (6, 10, 11).

Spontaneous regression has been documented in pediatric patients with LCH. Although spontaneous regression also occurs in adults with LCH, it is predominantly associated with pulmonary LCH and a history of smoking. Spontane-

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ous regression in MS-LCH, particularly with the involvement of organs at risk, is exceedingly rare, with few documented cases (12-14).

We herein report a case of MS-LCH in which the patient presented with a ruptured hepatic tumor along with multiple lung, liver, and pancreatic lesions. Despite the initial aggressive nature of the disease, the patient experienced spontaneous regression following smoking cessation without the need for chemotherapy.

Case Presentation

A 67-year-old man presented with pain in the right upper quadrant. He had a medical history of Sjögren's syndrome and psoriasis with no active treatment and hypothyroidism with levothyroxine supplementation. One week earlier, he had experienced lethargy and loss of appetite, followed by abdominal pain radiating to the back. The patient had smoked 1 pack of cigarettes per day for more than 40 years and had quit smoking upon admission.

His vital signs were as follows: body temperature 37.1°C, pulse 102 beats/min; blood pressure, 101/64 mmHg; and oxygen saturation, 97% while breathing ambient air. An abdominal examination revealed rebound tenderness in the upper right quadrant. Laboratory findings revealed a slightly elevated liver enzyme level and lactate dehydrogenase level of 324 U/L (reference value, 124-222 U/L). Other notable laboratory data included an elevated C-reactive protein level of 16.2 mg/dL (reference value, 0-0.14 mg/dL) with leukocytosis and no anemia, thrombocytopenia, or coagulation abnormalities. No abnormal cells were observed in peripheral blood smears.

Computed tomography revealed rupture of the liver tumor, measuring 45 mm in the S5/S6 region, as well as multiple masses of different sizes in the liver, lungs, and pancreas (Fig. 1a-e). The lung masses exhibited necrotic changes (Fig. 1). Metastatic hepatocellular carcinoma and pancreatic adenocarcinoma were suspected. However, an endoscopy-guided core biopsy of the pancreatic mass revealed proliferation of medium to large tumor cells with abundant eosinophilic cytoplasm, conspicuous nucleoli, nuclear atypia, and frequent mitotic figures (Ki-67>90%). Immunostaining was positive for S-100, CD1a, and Langerin (CD207), and negative for BRAF V600E, CD3, CD5, CD7, CD20, CD30, CD56, CD79a, PAX5, CD138, MUM-1, TdT, EBER, cytokeratin (AE1/AE3, MNF116), and SOX10 (Fig. 2), leading to a diagnosis of Langerhans cell neoplasm. A further evaluation of the lung mass via a biopsy yielded similar findings: proliferation of large highly mitotic cells with nuclear atypia. Immunohistochemistry revealed that these cells were positive for CD1a, S-100a, and Ki-67 (> 90%) and negative for CD3, CD20, CD79a, and AE1/3, indicative of Langerhans cell origin. Considering the high mitotic figures, nuclear atypia, and aggressive clinical features, a diagnosis of Langerhans cell sarcoma (LCS) was initially made. Intensive chemotherapy was initiated followed by allogeneic hematopoietic stem cell transplantation. To determine the stage for treatment initiation, fluorodeoxyglucose-positron emission tomography was performed three weeks after admission. Surprisingly, the multiple masses spontaneously regressed (Figs. 3a-e), leading us to reconsider the diagnosis of LCS. Following an in-depth discussion with the pathologists, it was observed that, despite the pathological findings indicating necrosis and high Ki-67 expression, there was minimal cellular atypia. Considering that spontaneous regression has never been reported in patients with LCS, we changed the diagnosis to MS-LCH.

As the tumors demonstrated a tendency to spontaneously regress, and the patient's general condition improved, we adjusted the treatment plan from intensive chemotherapy to watchful waiting. A week later, a biopsy of the liver mass, which had decreased in size from 45 to 30 mm, revealed extensive necrosis in most areas of the mass and low Ki-67 expression (Fig. 4). Following recovery from liver tumor rupture, the patient was discharged on day 31 after the first admission.

During monthly visits to the outpatient clinic, we conducted careful imaging follow-ups, including bi-monthly abdominal ultrasound and computed tomography. At the four-month follow-up, the masses continued to regress, with some completely disappearing following smoking cessation and watchful waiting (Fig. 5a and b). Currently, the patient is doing well.

Discussion

We encountered a case of MS-LCH in which the patient presented with rupture of a hepatic tumor and organs at risk including the liver and lungs. Remarkably, after cessation of smoking, the patient exhibited spontaneous regression without the need for chemotherapy. Given the extensive necrosis and high Ki-67 expression, in addition to mild cellular atypia, distinguishing between LCS and LCH is challenging. With limited literature, we carefully planned biopsies of each of the lesions, including the pancreas, lungs, and liver. During this period, the tumor began to regress spontaneously, allowing us to shift the treatment strategy from intensive chemotherapy to careful observation.

Distinguishing between LCH and LCS

Langerhans cell neoplasms are divided into LCS and LCH, depending on the degree of cytological atypia and clinical disease course. LCS is a high-grade neoplasm with Langerhans cell-like features that exhibits distinctive malignant cytological characteristics. It typically presents with more aggressive behavior and a worse prognosis than LCH. Currently, specific molecular markers for LCS have not been established, and the distinction between LCS and LCH relies on morphological phenotypes, such as nuclear atypia, mitotic figures, and clinical courses (15). Therefore, distinguishing between LCH and LCS can be challenging in certain cases.

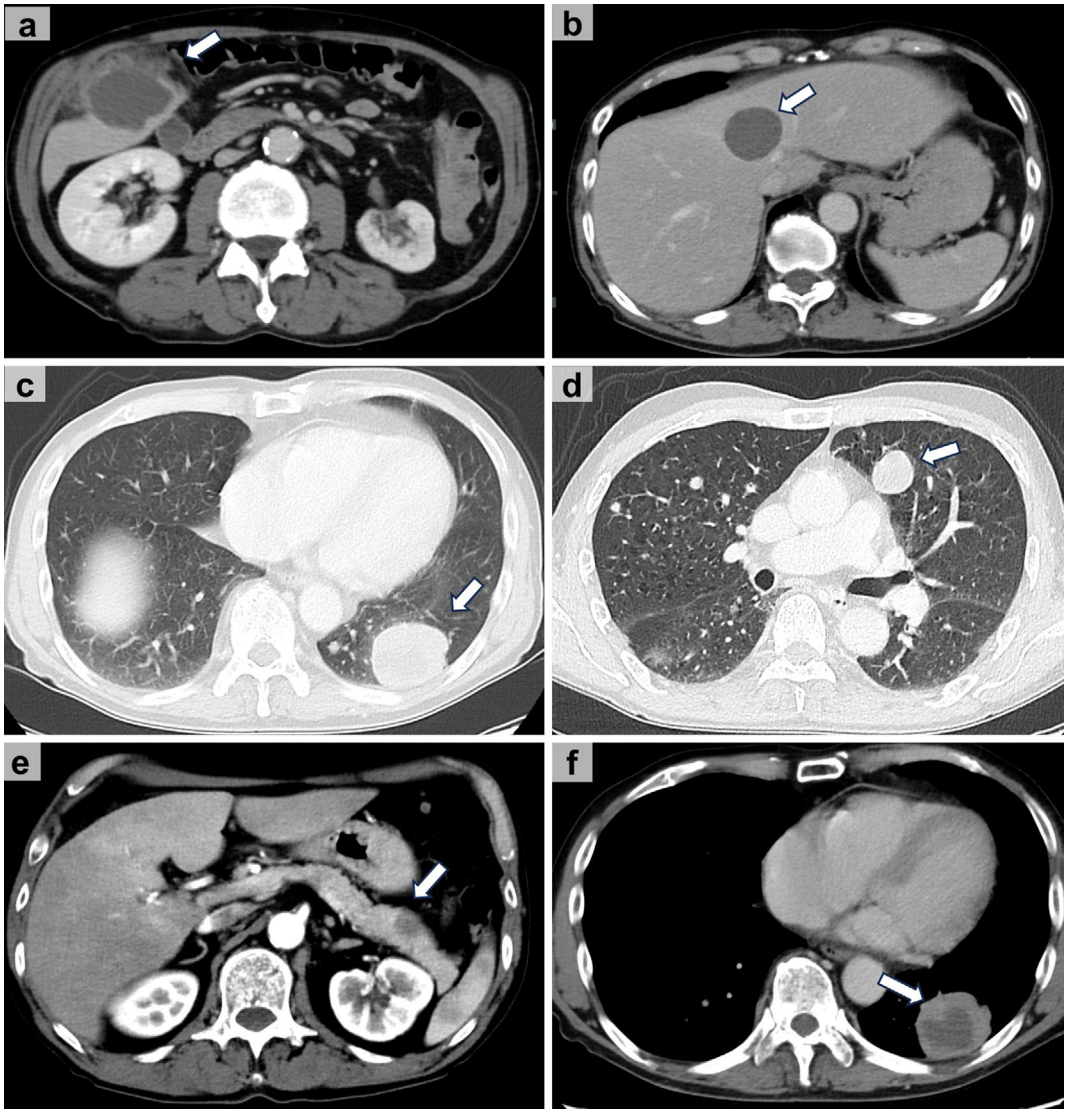

Figure 1. Computed tomography findings at initial presentation. (a) Rupture of a liver tumor measuring 45 mm in the S5/S6 region (white arrow). (b) Another liver mass (white arrow). (c-d) Multiple masses in both lungs (white arrow). (e) A mass in the tail of the pancreas (white arrow). (f) A lung lesion exhibiting necrotic changes, indicative of the aggressive nature of the tumor (white arrow).

In our case, extensive necrosis, a high Ki-67 expression (>90%), and mild nuclear atypia observed in the pathological examination of the pancreas initially led to a diagnosis of LCS. Given the unexpected spontaneous regression of multiple masses, we conducted a thorough discussion with pathologists. Considering that spontaneous regression has never been reported in LCS and that minimal cellular atypia does not strongly support LCS, we decided to change the diagnosis from LCS to MS-LCH. Previously, a similar case was reported in which an 89-year-old woman with left axillary lymphadenopathy was initially diagnosed with LCS based on morphological features, a high MIB-1 index, and multi-system involvement. However, the tumors regressed spontaneously without chemotherapy, 11 months after the initial presentation. In that case, the authors also changed the diagnosis to MS-LCH after spontaneous tumor regression (12). Several markers, including CD56 (16), p16 deletion (17), and IGF2BP3 (18), have been proposed to distinguish LCS from LCH in adults. In our case, the patient tested positive for IGF2BP3 and negative for CD56 and p16 deletions. Further research is necessary to determine the specificity of these markers.

Spontaneous regression in LCH

Our patient exhibited spontaneous tumor regression after smoking cessation. Spontaneous regression can also occur in adults with LCH and is predominantly associated with pulmonary LCH and smoking. Spontaneous regression in adult MS-LCH with the involvement of organs at risk is exceedingly rare, with only a few documented cases (12-14). To explore the characteristics of spontaneous regression of MS-LCH in adults (age >18 years old), we conducted a literature review and identified four cases, including ours (12-14) (Table). The ages of the patients ranged from 24 to 89 years old. The involved organs varied, including the lymph nodes, bone, lungs, and liver, with three cases involving at-risk or-

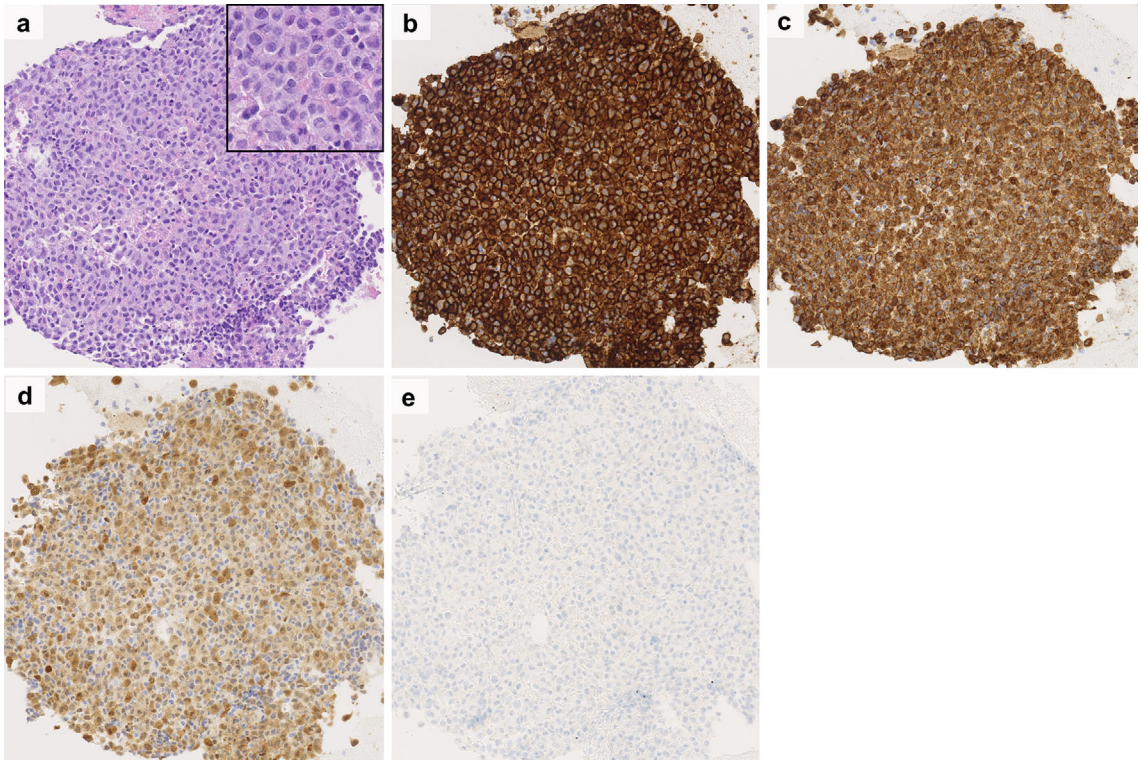

Figure 2. **Pathological analyses of the pancreatic lesion. (a) Hematoxylin and Eosin staining showing proliferation of medium to large-sized tumor cells with abundant eosinophilic cytoplasm and conspicuous nucleoli. (b-e) Immunohistochemical staining. (b) CD1a. (c) Langerin (CD207). (d) S-100. (e) BRAF V600E.**

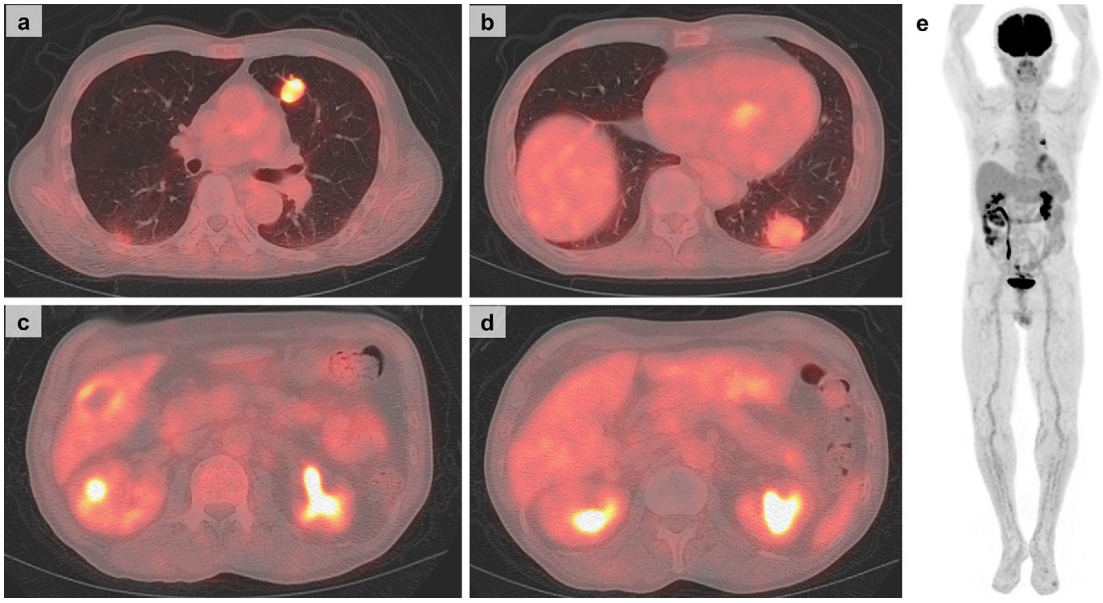

Figure 3. **Positron emission tomography-computed tomography (PET-CT) findings of the whole body. PET-CT identified several lung, liver, and pancreatic lesions, which had decreased in size compared to those on CT performed at the initial presentation. The FDG accumulation was relatively low, suggesting decreased tumor activity. (a-b) Lungs (SUVmax 3.4-7.4). (c) Liver (SUVmax 3.8). (d) Pancreas (SUVmax 2.6). (e) Whole body.**

gans. One case was investigated for the *BRAF V600E* mutation. The expression of CD56, a proposed marker for LCH with a poor prognosis, was examined in two cases and was negative in both instances. One patient was managed with watchful waiting, whereas the remaining three patients underwent smoking cessation. Tumor regression was initiated

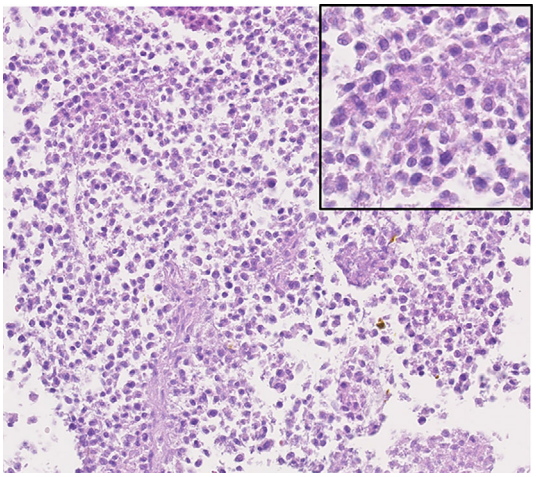

Figure 4. Pathological analyses of the hepatic lesion. Extensive necrosis in most parts of the mass is observed.

within 2 weeks to 18 months. In the extreme case (Patient 2), the regression continued for six years. In all three previously reported cases, a complete response was achieved. In the present case, while the current response was considered partial, the tumors continued to shrink at the six-month follow-up. Further data collection is necessary to identify clinical characteristics and specific markers of LCH that exhibit spontaneous regression.

While adults with pulmonary LCH can achieve spontaneous regression solely through smoking cessation, few cases suggesting the efficacy of smoking cessation and watchful waiting in MS-LCH with the involvement of organs at risk have been reported. This may be because chemotherapy is initiated immediately after the diagnosis, owing to the risk of organ damage, thereby making it impossible to evaluate the sole efficacy of smoking cessation.

Potential mechanism of tumor regression

The mechanism underlying spontaneous tumor regression after smoking cessation in patients with LCH remains elusive. Recent investigations have elucidated the role of the tumor microenvironment in the pathogenesis of LCH. One study revealed that constitutive activation of the MAPK pathway in multipotent hematopoietic progenitor cells results in cellular senescence, leading to apoptosis resistance and a senescence-associated secretory phenotype (SASP) (19). In turn, SASP triggers the subsequent infiltration of inflammatory cells, including T cells and eosinophils, eventually causing immune escape and tumor progression (20). Smoking may modulate inflammatory cytokines, such as those in the SASP. In our case, infiltration of immune cells, such as lymphocytes and eosinophils, was observed around the tumor, suggesting high immunogenicity. Immunohistochemistry was negative for programmed death ligand 1. Smoking cessation can contribute to the improvement of the tumor microenvironment, possibly leading to reactivation of immune cells and tumor regression. Further research is warranted to unravel the pathogenic role of smoking in LCH and its influence on the tumor microenvironment.

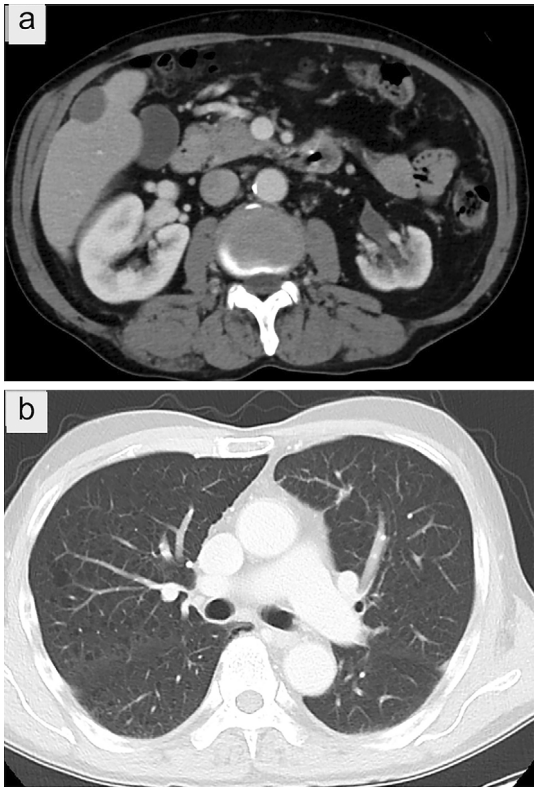

Figure 5. Regression of the lesions demonstrated on computed tomography. (A) Hepatic lesions regressed in size from 45 to 23 mm. (B) Lung lesions achieved almost complete remission. Please see Figure 1 for the comparison.

Clinical implications and future directions

The present case suggests that a distinctive subset of MS-LCH cases can be managed by smoking cessation and careful observation through follow-up imaging. Future investigations are necessary to identify specific markers of this subset. This case report challenges the current paradigm of immediate chemotherapy for MS-LCH with at-risk organ involvement. Despite its aggressive clinical features and organ damage at first presentation, there is a subpopulation of MS-LCH for which chemotherapy is not required, and remission can be achieved solely through smoking cessation.

Conclusion

We encountered a case of initially aggressive MS-LCH characterized by the involvement of organs at risk, specifically manifesting as a rupture of a hepatic tumor. Substantial regression of multiple lesions was achieved solely through smoking cessation. Despite the typically aggressive nature of these lesions and their association with at-risk organs, our findings highlight a distinct subset of MS-LCH that exhibits remission solely through smoking cessation. This observation prompts a reconsideration of treatment strategies, suggesting that careful observation through follow-up imaging

Table. Cases of Adult MS-LCH That Regressed Spontaneously through Smoking Cessation or Watchful Waiting.

Patient No.	Age	Sex	LCH type	Involved organs	Immunophenotyping	BRAF V600E	CD56	Treatment	Duration of regression	Outcome	Ref.
1	89	F	MS-LCH	multiple lymphadenopathies	CD1a (+), S100 (+), Langerin (+), CD68 (+), high MIB1 index	NR	negative	watchful waiting	2-6 months	CR	12
2	24	F	MS-LCH	bone, lung	CD1a (+), S100 (+)	NR	NR	smoking cessation	1-6 years	CR	13
3	34	F	MS-LCH	vertebra, lung	CD1a (+), S100 (+), Langerin (+)	NR	NR	smoking cessation	3-18 months	CR	14
4	67	M	MS-LCH	lung, liver, pancreas	CD1a (+), S100 (+), Langerin (+), high Ki-67 index	negative	negative	smoking cessation	2 weeks (ongoing)	PR	our case

LCH: Langerhans cell histiocytosis, MS-LCH: multi-system Langerhans cell histiocytosis, NR: not reported, CR: complete remission, PR: partial remission, Ref: reference

is a reasonable alternative to chemotherapy.

The authors state that they have no Conflict of Interest (COI).

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Statement of Ethics

Study approval statement: Not applicable.

Consent to publish statement: Informed consent was obtained from the patient for the publication of this case report.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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