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Case Report

High Dose Cladribine in Combination with High Dose Cytarabine as A Salvage Therapy for Adults with Refractory Relapsed Langerhans Cell Histiocytosis

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Abstract

Introduction

Langerhans cell histiocytosis (LCH) is a rare condition with extremely variable manifestations ranging from single-organ involvement to multisystemic dysfunction that can be refractory or relapse. Currently, no international standard care guidelines exist for treating adult patients with refractory, multisystem LCH. This case series describes three patients with refractory multisystem LCH who failed to respond to multiple lines of chemotherapy or radiotherapy but remarkably achieved sustained complete metabolic remission after treatment with a modified "pediatric-inspired" cladribine-based intensive induction (CLAG) protocol.

Presentation of Cases

Case 1 was a 29-year-old female who presented with chronic left thigh pain and an abnormal gait. Case 2 was a 39-year-old male who presented with a 2-year history of generalized body and back pain. Case 3 was a 21-year-old female who presented with increasing maxillary pain, night sweats, and weight loss. In all three cases, the initial radiological imaging showed osteolytic lesions and tissue biopsies confirmed the diagnosis of LCH. Case 1 received standard induction chemotherapy and two lines of salvage therapy before the CLAG protocol was initiated. Case 2 was treated with standard induction chemotherapy, and the CLAG protocol was used as first line salvage therapy. Case 3 was treated with standard induction chemotherapy and the CLAG protocol used as second line salvage therapy. In Case 1, maintenance therapy was stopped at 6 months due to recurrent infection and prolonged cytopenia. In Case 2, significant changes were made to the maintenance phase protocol because of side effects. The CLAG protocol resulted in complete metabolic remission in all patients based on follow-up PET/CT examinations.

Conclusion

We report 3 cases of refractory/relapsed LCH in adult patients who experienced complete metabolic remission following salvage chemotherapy using a modified CLAG protocol after failure of at least one line of standard induction therapy.

Keywords: Cladribine; Cytarabine; Langerhans Cell Histiocytosis; Osteolytic Lesions

Introduction

Histiocytosis X was renamed Langerhans cell histiocytosis (LCH) in 1987 and is a rare disorder with an unknown true incidence that is caused by abnormal proliferation of Langerhans cells resulting in the formation of granulomas [1,2]. The clinical manifestation of LCH is variable and ranges from infiltration of a single organ to multisystem infiltration; risk-organ involvement, which includes the hematopoietic system, liver, and/or spleen, carries a poor prognosis [1,2]. The most common site involved is the bone, with central nervous system (CNS) involvement being less common. The skull (predominantly the posterior jaw) followed by the femur, pelvis, and spine are the most frequent sites of skeletal involvement [3,4]. To the best of our knowledge, no international guidelines or studies have been published on the treatment of adult patients with refractory or relapsed LCH using a combination of cladribine and cytarabine (CLAG). This case series describes three patients with refractory multisystem LCH in whom we achieved sustained metabolic remission after treatment with a pediatric-inspired, dose-modified, CLAG-based therapy [5].

Clag Protocol

The pediatric CLAG protocol was first described in a Phase II clinical study and included at least two 5-day courses of cytarabine (1 g/m2 per day) plus cladribine (9 mg/m2 per day). In addition, maintenance therapy consisted of two 3-day courses of cladribine (5 mg/m2 per day) followed by vinblastine (6 mg/m2) every 2 weeks for 6 months, combined with oral prednisolone (40 mg/m2) for 5 days every other week, oral 6-mercaptopurine (6MP) (50 mg/m2) every day, and oral methotrexate (MTX) (20 mg/m2) once per week. Oral 6MP and MTX were continued for an additional 12 months.5

Case Reports

Case 1

Case 1 was a 29-year-old female patient who initially presented to another facility with complains of persistent left thigh pain and walking with a limp in April 2005. She was seen by an orthopedic team, and a plain radiograph of the left femur showed the presence of multicentric multifocal osteolytic lesions in the shaft of the left femur with significant cortical destruction; however, other clinical examination findings were unremarkable. Laboratory workup revealed mild anemia. Skeletal survey & bone scanning noted multiple osteolytic lesions in the ischial bones, both parietal bones, and the C4 cervical vertebra. On the 20th of April 2005, she underwent surgical revision and excision of the bony lesions and prophylactic open reduction with internal fixation using plates & screws. Histopathological examination of the tissue biopsy confirmed LCH. Initial induction therapy and surgical intervention were selected based on the multifocal nature of the patient's disease upon presentation as described in Table 1. Following this treatment regimen, the patient achieved first remission and became pregnant 2.5 years after the end of her treatment. In 2008, she developed severe persistent low back pain. Computed tomography (CT) showed localized disease with destruction of the T11 vertebra that was treated with direct field high-energy beam radiotherapy [Table 2]. Afterwards, her pain significantly improved. In 2009, she presented with pain in the right arm. A bone scan revealed a destructive lesion in the right humerus. Contrast-enhanced PAN-CT showed multiple osteolytic lesions in the dorsal, lumbar, and pelvic regions. Radiotherapy and surgery were initiated as described in Table 2. The patient remained progression-free until 2010 when positron emission tomography (PET)-CT imaging revealed widespread increased uptake in the right frontal-parietal and occipital bones, right humerus, right iliac crest, left femur, and several vertebrae. First line salvage chemotherapy according to Histiocytosis Society Protocol type-II was initiated, as outlined in Table 2. Upon radiological evaluation, the patient showed a promising response. During a clinic visit in 2014, the patient complained of a progressive swelling in her right neck. A whole spine MRI was conducted, and this revealed a soft tissue infiltrating lesion extending from the left side of the neck into the neural foramina and spinal canal at C2–C4 vertebral levels. A biopsy indicated that the mass was consistent with LCH. Owing to impending cord compression, the patient was placed on intravenous (IV) dexamethasone [Table 2] and subsequently became stable and asymptomatic. Additional chemo- and radiotherapy were initiated [Table 2], but a PET-CT scan showed interval disease progression with multiple new bone lesions and intense muscular uptake in both rotator cuff muscles. The patient was started on chemotherapy according to the LCH 2009 protocol [Table 2]. The follow-up PET/CT after two courses of the LCH 2009 protocol revealed no significant changes, and only one bone lesion involving the left ischium showed significant reduction in its maximum standardized uptake value (SUV) from 9.4 to 3.6 [Figure 1]. Additionally, a right axillary nodal mass biopsy was performed, and immunohistochemistry was positive for CD1a, S100, and langerin, all of which are consistent with LCH [Figure 2]. As the patient did not show a meaningful response to cytarabine therapy and the LCH 2009 protocol, the new pediatric-inspired CLAG protocol was initiated as third-line salvage therapy. The patient received the first and second cycles of the CLAG protocol including cladribine at a dose of 5 mg/m2 along with 500 mg/m2 of cytarabine [6]. Follow-up PET/CT showed findings suggestive of a good partial response [Figure 3A]. After receiving a third cycle of the CLAG protocol, the patient attained complete remission. The maintenance phase was initiated as described in Table 2. The patient was not able to tolerate this phase for long due to frequent episodes of febrile neutropenia and hepatotoxicity. Follow-up PET/CT at the end of therapy showed findings suggestive of a complete metabolic response [Figure 3B]. Follow-up PET in September 2018 revealed complete metabolic remission. A follow-up CT scan in March 2020 still indicated complete metabolic remission [Figures 3C, 3D].

Table 1: Case 1 treatment overview.

	Medical	Surgical
Initial	Vinblastine qw × 6 months Steroids External irradiation 20 Gy, 10 fractions	Excision of lesions: prophylactic open reduction and internal fixation
Relapse 2008	Direct field high-energy beam (20 Gy, 10 fractions)	
Relapse 2009	Radiotherapy	Curettage with bone chip insertion Internal fixation

Relapse **First salvage** **2010**	5-day prednisone IV etoposide Vinblastine 3 times qw × 6 months	
Relapse **Second salvage** **2014**	4 mg IV dexamethasone Radiotherapy (20 Gy, 10 fractions) Cytarabine, 5 cycles (100 mg/m^2 × 5 days) LCH protocol 2009 (vinblastine, prednisolone) × 2	
Third line salvage	CLAG, 3 cycles Maintenance: cladribine 2 cycles, IV vinblastine, steroids, 6MP, MTX	
CLAG maintenance details: 2 cycles of cladribine (5 mg/m^2) for 3 days every 21 days. Then, IV vinblastine (6 mg/m^2) + steroid for 5 days q2w, 6MP qd, and MTX qw for a total of 12 months. qw = weekly, qd = daily, 6MP = 6-mercaptopurine, MTX = methotrexate, IV = intravenous, CLAG = cladribine-based intensive induction, LCH = Langerhans cell Histiocytosis.		

Table 2: Overview of case details at first presentation.

	Medical History	**Presentation**	**Diagnostic Assessments**	
			Radiology	**IHC**
Case 1 **(2005)**	• Female,29 y • No previous hematological/malignant disease • Uncle: NHL	• Unable to conceive 4+ years • Chronic left thigh pain • Limping	multiple osteolytic lesions – ischium, skull, cervical spine	S100 protein+ CD68+ (Lymph node form the right axilla)
Case 2 **(2014)**	• Male, 39 y • No personal or family history of hematological neoplasm	• Generalized body and back aches 2 years	Figure 6: • T10 fracture • T5 to L5 osteolytic lesions	S100, CD1a, and Langerine ++ (Soft tissue of the anterior mandible)
Case 3 **(2011)**	• Female, 21 y	• Increasing maxillary pain • Night sweats • Weight loss of 6 kg over 4 months	CT: • Multifocal lytic temporal bone lesions	CD68+ CD1a+ S100 protein+ (left maxillary sinus and left mandible angle)
y.o, years old; NHL, non-Hodgkin lymphoma; CT, computer tomography; T, thoracic; L. lumbar; IHC, immunohistochemistry.				

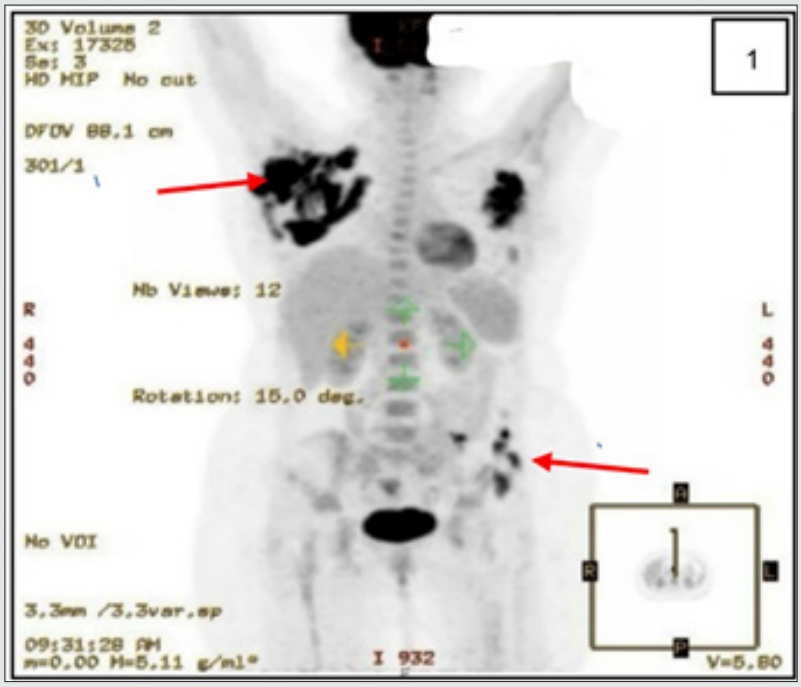

Figure 1: Case 1: Multiple lytic lesions involving the left pelvic bone, bilateral rotator cuff muscles, and left ischium. The left ischial lesion demonstrates a significant reduction in SUVmax from 9.4 to 3.6.

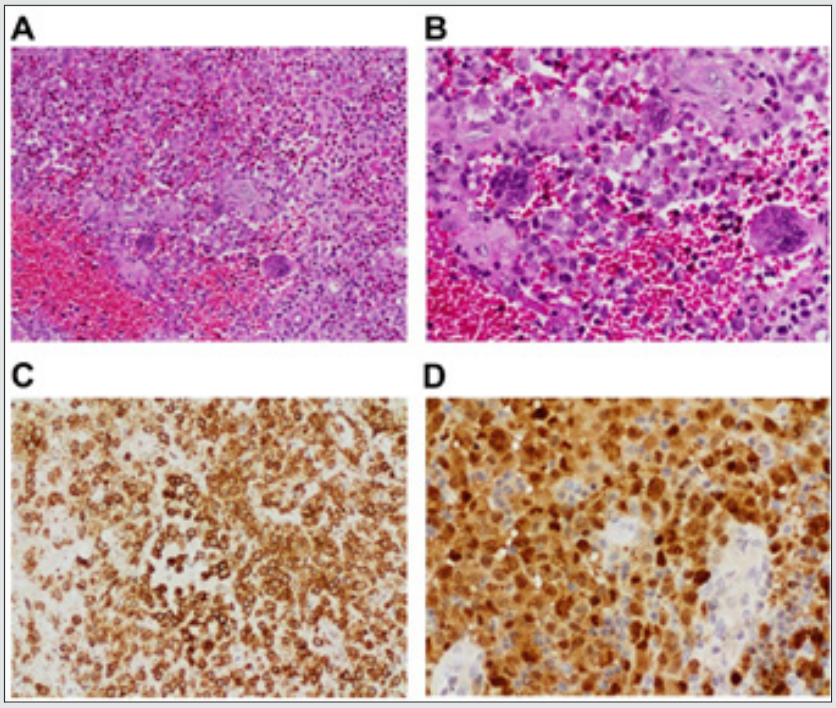

Figure 2: Case 1: Results from the histopathological examination. (A): Neoplastic tissue shows infiltrative polygonal cells with bright, abundant eosinophilic cytoplasm mixed with multiple eosinophils, lymphocytes, and neutrophils (×20). (B): Target cells containing longitudinal grooves with well-formed multinucleated giant cells (×40). (C): Immunohistochemistry shows diffuse positive staining for CD1a (×20) and diffuse positive staining for S100 protein (D, ×20).

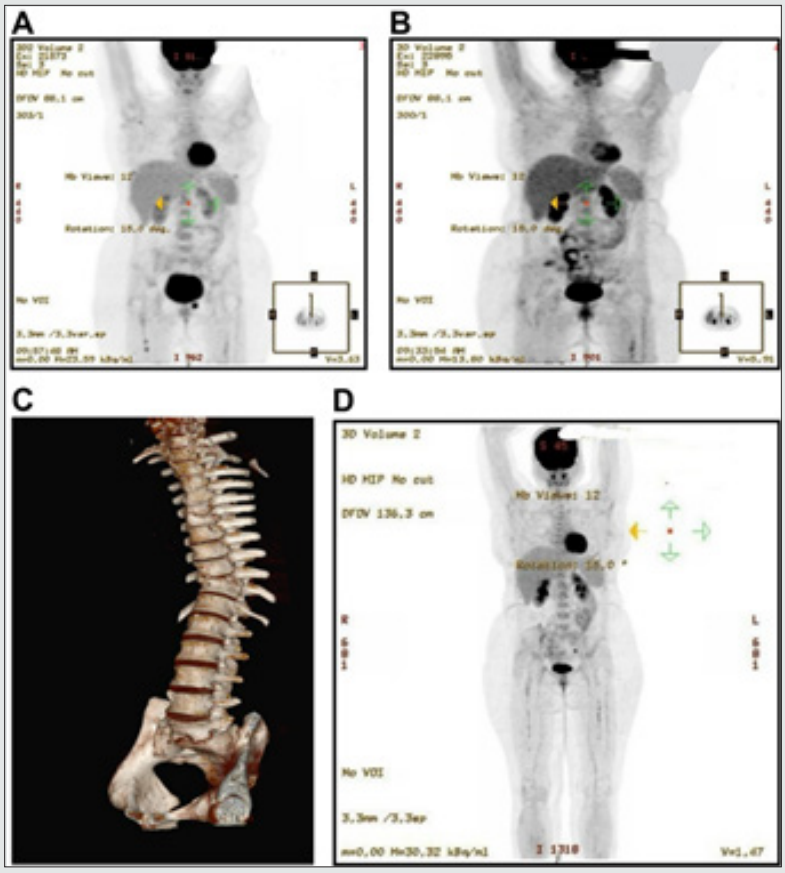

Figure 3: (A): Appearances are suggestive of a particularly good partial response to treatment in Case 1. (B): Scan appearances suggestive of a complete metabolic response. (C): Findings are consistent with no signs of disease relapse.

Case 2

Case 2 was a 39-year-old male patient who presented with bone pain and difficulties in walking for 2 years prior to presentation. On radiological imaging, we found a pathological fracture of T10 vertebra and osteolytic lesions in the thoracolumbar vertebrae involving T5 to L5. Tissue biopsy confirmed the lesion to be LCH. He initially received vinblastine and steroids at the referring hospital for approximately 1.5 years. The patient's characteristics at presentation and diagnosis are described in Tables 2, 3. He was refractory to initial treatment and was referred to us for further evaluation and management in 2015. We performed a spinal MRI which revealed multilevel lytic vertebral and bone lesions with complete loss of the T10 vertebra, as well as wedge fractures and vertebral body fusions at T5, T6, T10, and T11 vertebrae without of features suggestive of significant spinal canal stenosis or cord compression [Figures 4A, 4B and 4C]. A CT scan also revealed mandibular lesions. Histopathological examination of tissue biopsy specimens revealed Actinomyces infection in the soft tissue of the anterior mandible, along with LCH [Figures 5A-D]. BRAF mutation testing was negative. The patient was evaluated by the infectious disease team and was started on a prolonged course of oral and intravenous antibiotics. An urgent PET/CT revealed diffuse fluorodeoxyglucose (FDG)-avid bone involvement [Figure 6A]. Therefore, in March 2017, the patient was treated with the pediatric-inspired CLAG protocol as first line salvage chemotherapy. Both the first and second cycles of the induction phase were complicated by mild transaminitis and culture-negative febrile neutropenia. Following antibiotic treatment, the patient underwent a PET/CT scan, which demonstrated a favorable complete response to treatment [Figure 6B]. The patient was admitted for the third cycle of the CLAG protocol, which was complicated by febrile neutropenia secondary to bacteremia. Eventually, the patient was started on the maintenance phase of the protocol. During maintenance, he developed disseminated herpes zoster infection. Per patient preference, the 6 MP and MTX treatments were discontinued after 1 month, vinblastine and steroids was continued. Subsequently, a modified maintenance regimen was initiated, lasting for a total of 12 months [Table 3]. The last PET/CT scan was conducted in September 2020, and this showed no evidence of FDG-avid bone disease [Figure 6C].

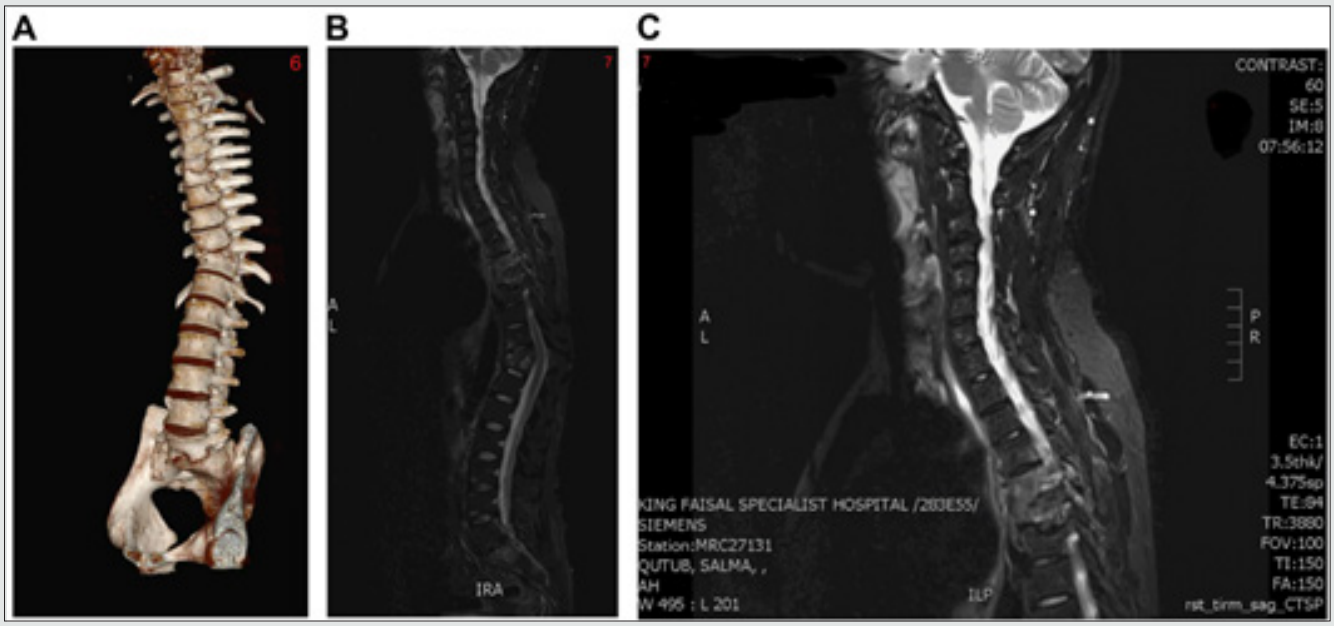

Figure 4: (A): Pathological fracture of the T10 vertebra and osteolytic lesions in thoracolumbar vertebrae T5–L5 in the Case 2 patient. (B): Multilevel vertebral body lytic and sclerotic bony lesions with complete loss of the T10 vertebral body without evidence of significant canal stenosis or cord compression (C).

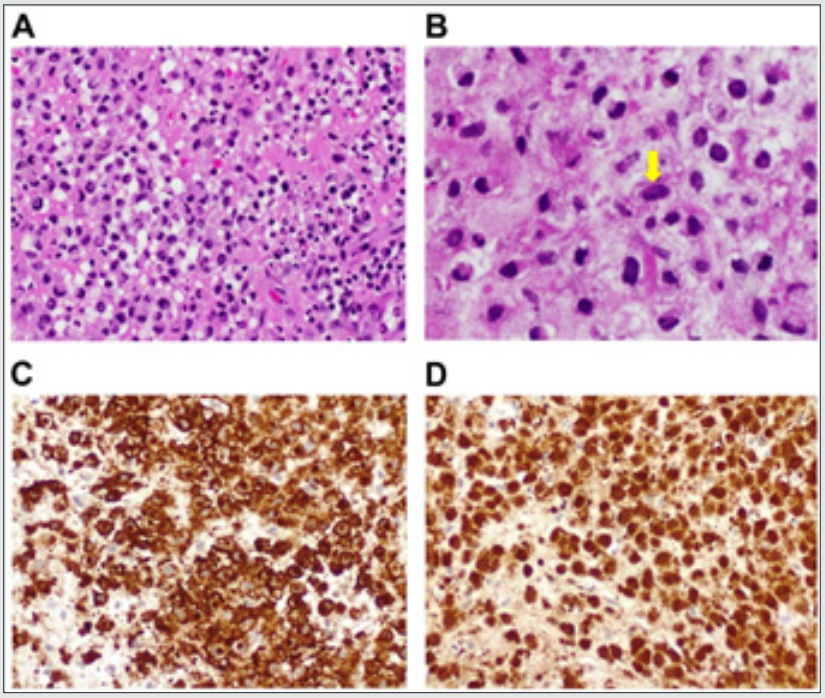

Figure 5: Case 2: Results from the histopathological examination. (A): Neoplastic tissue shows infiltrative polygonal cells with eosinophilic cytoplasm mixed with lymphocytes and neutrophils (×20). (B): Target cells contain oval nuclei with longitudinal grooves that resemble coffee beans (yellow arrow) (×40). (C): Immunohistochemistry showing diffuse positive staining for CD1a (×20) and diffuse positive staining for S100 (D, 20x).

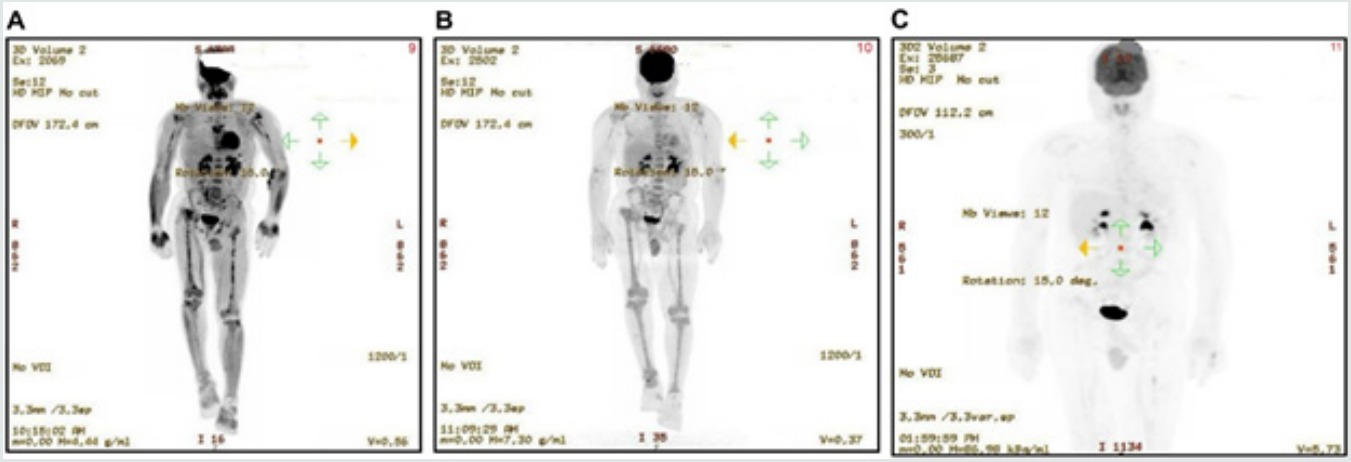

Figure 6: (A): Diffuse FDG-avid bony disease involvement, indicating active disease in Case 2. (B): Results indicating a favorable response to treatment. (C): No evidence of FDG-avid lesions in keeping with disease remission.

Table 3: Case 2 treatment overview.

	Medical	Surgical
Initial	Vinblastine + steroid 18 months	Excision of lesions: prophylactic open reduction and internal fixation
Relapse **First salvage**	CLAG, 3 cycles Maintenance: cladribine 2 cycles, IV vinblastine, steroids 6MP + MTX	
Modified CLAG maintenance details: vinblastine (6 mg/m^2) and prednisone (40 mg/m^2) for 5 days q4w (instead of q2w), continued for 12 months instead of 6 months. 6MP and MTX were discontinued after 1 month only q4w = every 4 weeks, 6MP = 6-mercaptopurine, MTX = methotrexate, IV = intravenous, CLAG = cladribine-based intensive induction.		

Case 3

Case 3 was a 21-year-old female patient who presented in May 2011 with complains of increasing maxillary pain and night sweats associated with g weight loss of approximately 6 kg within the previous four months. A skeletal survey showed multiple lytic lesions involving the skull and the right femur. CT scans of the chest, abdomen, and pelvis were normal, but a maxillofacial CT performed on the 28th of March 2011 revealed multifocal osteolytic lesions within the facial bones. LCH was confirmed based on histological examination findings of biopsy specimen taken from the left maxillary sinus and the angle of the left mandible on the 17th of April 2011. The biopsy specimen was also positive for CD68, CD1a, and S100 protein, and showed a focal area with marked fibrosis and chronic inflammation that was suggestive of LCH. A brain MRI conducted on the 11th of May 2011 showed temporal bone lesions suggestive of histiocytosis with no evidence of brain parenchymal involvement. The patient was diagnosed with LCH in 2011, and systemic induction therapy was started as described in Table 4. Following induction therapy, the patient reported complete pain relief and her overall clinical condition was satisfactory. Radiology confirmed improvement of the lesions in the right temporal and left maxillary bones. At a follow-up visit in 2012, she complained of right leg pain. A nuclear study confirmed recurrence of the disease in the right femur, which was treated with local radiotherapy along with low doses of prednisolone. The patient remained well until 2015 when she started to complain of recurrent jaw pain and was found to have a new lytic lesion in the temporomandibular joint and right femur. Following a CT scan, the first line of salvage therapy was started as described in Table 4. The patient suffered an LCH relapse that was confirmed by tissue biopsy [Figures 7A, 7B, 7C, and 7D] in 2016. Due to the refractory nature and disseminated involvement of her disease [mandibular alveolar ridge lesion and two ribs] [Figure 8A], she was not considered a candidate for radiotherapy and the CLAG protocol was initiated as second line salvage therapy [Table 4]. A PET-CT was conducted after the completion of the second cycle, which confirmed a complete response [Figure 8B]. The patient continued maintenance chemotherapy as per the CLAG protocol for 12 months. During the follow-up PET/CT scan in 2018, the patient

showed possible new lytic lesions involving the left iliac region and the right acetabulum [Figure 8C]. The patient was clinically asymptomatic and was heavily pretreated with chemotherapy and zoledronic acid [Table 4]. The tumor board decided to do a follow-up PET scan. Fortunately, a repeated PET/CT in September 2019 and another done after 6 months showed no evidence of residual disease [Figure 8D].

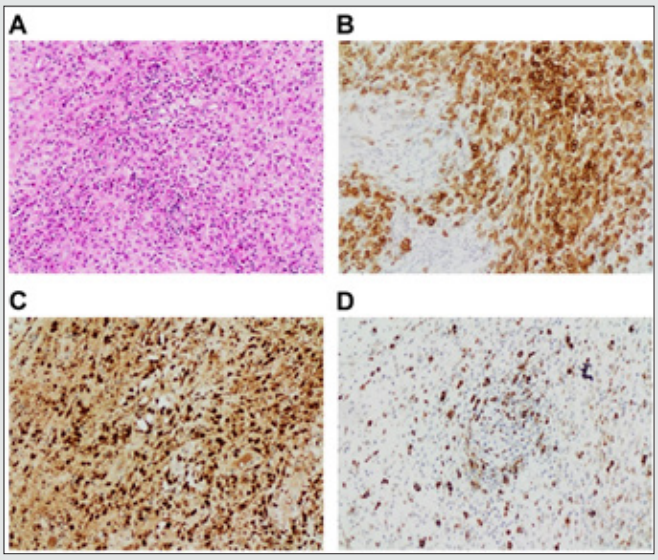

Figure 7: Case 3: Results from the histopathological examination. (A): Infiltrative polygonal cells with abundant eosinophilic cytoplasm mixed with eosinophils, lymphocytes, and neutrophils (×20). (B): Immunohistochemistry showing diffuse positive staining for CD1a (×20), diffuse positive staining for S100 protein (C, ×20), and CD68 highlights adjacent reactive histiocytic cells (D, ×20).

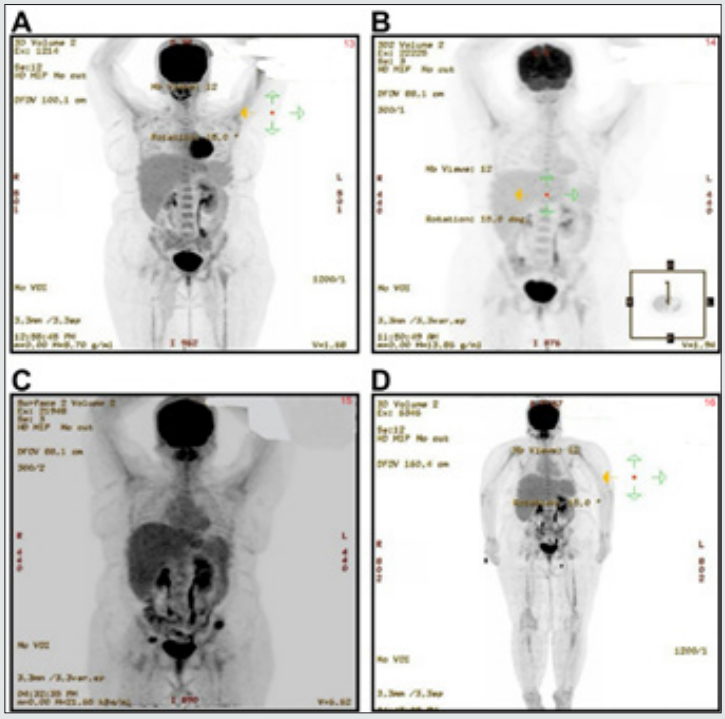

Figure 8: (A): Focal uptake (SUVmax 1.3) in the right anterior third and left anterior eight ribs of the patient in Case 3. (B): No evidence of FDG uptake suggestive of a complete response. (C): New lytic lesions involving the left iliac region and the right acetabulum. (D): No evidence of FDG-avid lesions, in keeping with disease remission.

Table 4: Case 3 treatment overview.

Medical	
Initial	Systemic chemotherapy • Vinblastine qw • Oral prednisolone 6 months
Relapse 2012	Localized radiation Low dose prednisolone
Relapse 2015 First salvage	Cytarabine 100 mg/m^2 for 5 days, monthly for 6 cycles
Relapse 2016 Second salvage	CLAG
Relapse 2015	Chemotherapy IV zoledronic acid (4 mg monthly)
CLAG maintenance details: 2 cycles of cladribine (5 mg/m2) for 3 days every 21 days. Then, IV vinblastine (6 mg/m2) + steroid for 5 days q2w, 6MP qd, and MTX qw for a total of 12 months. q2w = every 2 weeks, qw = weekly, qd = daily, 6MP = 6-mercaptopurine, MTX = methotrexate, IV = intravenous, CLAG = cladribine-based intensive induction.	

Discussion

To the best of our knowledge, this is the largest reported case series of refractory LCH in adult patients that was treated with a modified CLAG regimen after failure of at least one line of standard chemotherapy. The patients in this series were from Saudi Arabia. The age at diagnosis ranged from 21 to 39 years. Two patients had multisystem LCH involving the musculoskeletal system with CNS involvement, and all patients had refractory disease or experienced relapse after standard induction chemotherapy. Our patients had no lesions in "risk organs" including the bone marrow, spleen, or liver. The time between the initial diagnosis and commencement of the CLAG protocol was at least 3 years in Cases 2 and 3 and more than 10 years in Case 1. In all cases, the patients experienced febrile neutropenia with septicemia and prolonged pancytopenia (grades 3-4 as per the World Health Organization grading) after administration of the CLAG protocol and required supportive care with transfusion of blood product along with granulocyte-colony stimulating factor, and prolonged hospitalization. None of the patients required admission into the intensive care unit. Nevertheless, our patients achieved complete remission based on their clinical and radiological response. The use of cladribine as a single agent has been reported since the 1990s. It has been successfully used in many patients and is considered the standard therapy for patients with multifocal bone disease [7,8]. A handful of studies have reported the use of high dose cladribine and cytarabine in pediatric patients. Rosso et al presented a retrospective study of nine pediatric patients, of which seven achieved complete remission after treatment [9]. Pant et al reported on a single-case study of an 8-month-old infant who had relapsed while receiving vinblastine and prednisolone but similarly had responded well to the CLAG protocol [10].Side effects, such as febrile neutropenia, anemia, and thrombocytopenia have also been documented in these studies and should also be anticipated after using the CLAG protocol in adults [9-12]. Severe toxicity should be taken seriously to avoid premature discontinuation of the protocol, and it is recommended that intense chemotherapy should only be administered in centers that are experienced in the management of severe toxicity, capable of providing adequate supportive care, and are trained in providing AML chemotherapy [12]. Many pediatric trials have shown that using cladribine as a monotherapy is effective for low-risk recurrent disease, and as per the current Histiocyte Society LCH IV protocol, it is used as second- or third-line salvage therapy [13-15]. treatment outcomes were also particularly unfavorable in patients who had risk-organ involvement based on the LCH-S-98 protocol for refractory cases [16-20]. The CLAG protocol used in this study was first presented in an international Phase II pediatric study published in 2015.6 The study showed promising results for refractory patients with an overall response rate of 92% and an overall survival rate of 85% [6-21]. Here we report a case series of three adult patients with refractory multisystem LCH who were treated with the pediatric-inspired intensive CLAG protocol. However, in some patients, changes to the protocol, including dose modification, were required. In Case 1, the maintenance therapy was stopped at 6 months instead of at 12 months because of repeated hospitalization for recurrent infection and prolonged cytopenia. In Case 2, a significant change to the protocol was made during the maintenance phase because of the side effects of MTX and 6MP, both of which were discontinued. Treatment with vinblastine and a steroid continued for 12 months instead of 6 months. Case 3 received a full course of treatment as per the CLAG protocol. These changes further illustrate the toxicity issues arising from this type of intense chemotherapy and the importance of establishing adequate dose modification and toxicity management guidelines. While it would be beneficial for both patients and clinical staff to avoid treatments with widespread toxicity, the options for patients with refractory multisystem LCH are extremely limited. For 30 years, several

different therapies for multisystem LCH have been tested, ranging from light to intensive chemotherapy resulting in only minor advances [22]. The predominant treatment strategy includes prednisone as a single agent or in combination with vinblastine. The LCH-III trial showed that prolonging therapy with vinblastine and prednisone in patients with multisystem LCH for at least 12 months was effective and associated with improvement in the survival rate of up to 84% and a decrease in the 5-year relapse rate to 27% [23]. The LCH-I randomized study was performed in patients with multisystem LCH without risk-organ involvement who were treated with either vinblastine or etoposide. While this combination proved efficacious, vinblastine and prednisolone was preferred because of the increased risk of secondary leukemia associated with using etoposide [24]. As an alternative, Abla et al. suggested the use of cytarabine [100-170 mg/m2 daily over 3–5 days every 3–4 weeks] as a single agent salvage chemotherapy [25]. A number of studies found that switching to salvage therapy early in patients with a slow response to initial induction therapy and providing more efficient salvage regimens resulted in better outcomes [22-27]. Although most patients will attain a complete response, approximately 50% of patients will either be unresponsive to treatment or relapse. Patients without risk-organ involvement tend to have favorable outcomes, whereas those with multisystemic disease and risk-organ involvement tend to be more difficult to treat and require intensified treatment that still results in poor outcomes [28]. For the cases presented here, the initial induction therapy was vinblastine and a steroid, with the duration ranging from 6 months in two patients [Case 1 and 3] to 18 months in one patient [Case 2]. Cladribine is a deoxyadenosine nucleoside analog that is converted to its triphosphate moiety following intracellular phosphorylation. The triphosphate moieties can be incorporated into both DNA and RNA during synthesis, and this results in the inhibition of enzymes, such as ribonucleotide reductase and DNA polymerase, ultimately resulting in the inhibition of proliferation and promotion of apoptosis [29-31]. In combination with cytarabine, the activating effect of cladribine on deoxycytidine kinase results in increased phosphorylation, activation, and accumulation of cytarabine [32]. Other nucleoside analogs, such as clofarabine, have also been assessed for their efficacy in the treatment of refractory pediatric LCH with results that are comparable to those of cladribine [33,34]. A Phase II clinical trial for the evaluation of clofarabine as a treatment for adult patients with recurrent or refractory LCH is currently recruiting subjects in the United States and in Canada [35]. In the last decade, our understanding of the histopathology of LCH has improved, and after the discovery of somatic mutations of the BRAF V600E gene in 65% of LCH cases, analysis of this gene has become part of the standard care. Although BRAF assessment is not yet included as a part of risk stratification, almost 50% of LCH patients with BRAF mutation become refractory or experience relapse to initial treatment and experience more aggressive disease, with a majority relapsing within the first 2 years after diagnosis [26,27]. Unfortunately, the BRAF V600E gene was only analyzed in Case 2, who was negative for mutations. While BRAF inhibitors, such as vemurafenib have been examined as a treatment option for LCH, the high rates of resistance and potential risk of cutaneous and pancreatic cancers seen in patients with BRAF-V600E-mutated melanoma following monotherapy with a BRAF inhibitor are a cause of concern [36]. Combined approaches with BRAF and MEK inhibitors have been evaluated in sporadic studies,12 and based on the results presented here, assessment of a combination of cladribine or CLAG and a BRAF inhibitor could be another useful avenue of investigation.

Conclusion

Despite some limitations in the treatment protocol and number of patients, we found that an AML-type CLAG-based intensive regimen can be effective and generally safe in adult patients with refractory or relapsed LCH, especially if introduced early, and resulted in complete metabolic remission in all our patients based on follow-up PET/CT examinations. Caution is warranted as this type of intensive chemotherapy is associated with recurrent febrile neutropenia, hepatotoxicity, and other infectious complications as shown in our patients. Our study indicates that the combination of high dose cytarabine and cladribine could be an effective salvage therapy in the treatment of adult patients with relapsed or refractory LCH and warrants continued examination of the CLAG protocol in expanded cohorts of adult patients including those with high-risk lesions.

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Disclosure

The author reports no conflicts of interest in this work.

Ethical Approval and Informed Consent

The institutional review board of our institution approved this study, and written informed consent was obtained from all the patients.

Consent for Publication

Written informed consent was obtained from the patients for the publication of their case details and accompanying images.

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Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, medical records review, data collection and entry, data analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing

the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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