ORIGINAL RESEARCH

Effectiveness and Safety of Low-Dose Radiotherapy in Eosinophilic Lymphoid Granuloma

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ABSTRACT

Objective • To investigate the efficacy and safety of low-dose radiotherapy in treating eosinophilic lymphoid granuloma.

Method • This study included a total of 20 patients diagnosed with eosinophilic lymphoid granuloma. All patients underwent low-dose three-dimensional conformal intensity-modulated radiotherapy for their lesions. We analyzed the control status of the lesions and any adverse reactions related to radiotherapy.

Results • The overall effectiveness of low-dose radiotherapy in treating eosinophilic lymphoid granuloma was 90%. The incidence of grade I and grade II adverse reactions induced by radiotherapy was 70% and 30%, respectively. Over a median follow-up period of 23.6 months, all patients showed controlled lesions within the target delineation of radiotherapy. After radiotherapy, four patients experienced occasional pruritus, and one patient had a recurrence outside the target area three years later. No long-term severe adverse reactions related to radiotherapy were observed during the follow-up period.

Conclusions • Low-dose radiotherapy demonstrates an apparent therapeutic effect on eosinophilic lymphoid granuloma with acceptable adverse reactions. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Eosinophilic lymphoid granuloma (ELG), historically known as Kimura disease, is a rare and benign medical condition with an exciting history dating back to the late 19th century.[1] This disease was first preliminarily reported in 1937, but its systematic description and understanding were significantly advanced by Dr. Kimura in Japan in 1948.[1,2] ELG can occur at any age, especially in young Asian males, and is characterized by subcutaneous masses, predominantly in the salivary glands, soft tissues, and lymph nodes.[2]

The clinical manifestations of this condition encompass a range of skin-related symptoms, including pruritus, roughness, and desquamation, with some patients additionally presenting eczema and rash.[3] In rare cases, these lesions may lead to complications such as bleeding, necrosis, ulceration, infection, and even damage to adjacent tissues and organs, with the underlying mechanisms remaining elusive. The diagnostic process for ELG relies on several objective indicators, including clinical manifestations, laboratory examinations, and histological characteristics. Notably, the clinical symptoms are often nonspecific and can lead to misdiagnosis,[4] highlighting the necessity of thorough pathological examination in establishing a definitive diagnosis.

Histologically, ELG is characterized by benign hyperplasia of eosinophilic lymphocytes, a feature that distinguishes it from lymphoma and other diseases.[5] In patients with ELG, elevated serum eosinophil counts and proportions are commonly observed, often accompanied by increased levels of IgE.[6] Despite various treatment approaches that have been employed, the overall efficacy in managing ELG has proven to be less than satisfactory.

Low-dose radiotherapy, often employed in the treatment of various medical conditions, has gained recognition for its diagnostic value in evaluating diseases, particularly in cases where conventional imaging techniques fail. This technique offers precise insights into the localization and characterization of lesions, aiding in the accurate assessment of disease extent and progression. Its potential as both a therapeutic and diagnostic tool underscores its significance in modern

Table 1. Clinical Data of 20 Patients With ELG

Case	Gender	Age	Disease Course (year)	Lesion Site	Lymph Node Involvement	Clinical Manifestation	Peripheral Blood		Lesion Size (cm^3)	Other
							EBC ($x10^9$/L)	Serum IgE (IU/mL)		
1	M	28	4	Right parotid	Yes	Pruritus and hypoproteinemia	3.48	6,360	339.87	Urine Protein (+)
2	M	33	4	Left cheek and parotid	Yes	Skin pruritus and roughness	1.08	1,580	137.69	
3	M	37	8	Right cheek	Yes	Skin pruritus and roughness	0.610	1,230	279.41	
4	M	30	5	Left parotid	Yes	Skin pruritus and roughness	0.420	194	63.06	
5	M	28	2	Right parotid and cheek, left temporal region	Yes	Skin pruritus and roughness	0.740	1,880	81.93	
6	M	30	4	Left temporal region	No	Pruritus	0.89	5,750	107.92	
7	M	83	4	Right parotid	Yes	Skin pruritus and roughness	0.51	5,290	363.95	
8	M	30	17	Bilateral parotid	Yes	Pain and pruritus	6.450	23,790	92.3	
9	M	59	10	Left cheek	No	Skin pruritus and roughness	0.910	6,840	67.39	
10	M	59	10	Right upper arm	Yes	Pruritus	0.580	7,170	306.9	
11	F	56	4	Right parotid	No	Skin pruritus and roughness	0.900	509	41.45	
12	M	48	8	Bilateral parotid	No	Skin pruritus and roughness	1.66	3,070	44.71	
13	M	44	7	Left parotid	Yes	Skin pruritus and roughness	1.35	1,720	303.53	
14	M	57	3	Right cheek	Yes	Skin pruritus and roughness	0.32	130	307.83	
15	F	37	5	Bilateral parotid	Yes	Pruritus	1.59	32,200	106.11	Anemia
16	M	44	0.5	Left parotid	No	Skin pruritus and roughness	1.090	1,060	58.56	
17	M	38	6	Left parotid	Yes	Pruritus	1.65	1,240	256.43	
18	M	19	10	Bilateral cheek	Yes	Pain and pruritus	0.66	2,310	92.78	
19	M	28	12	Right parotid	Yes	Skin pruritus and roughness	2.68	2,070	40.26	
20	M	67	4	Right parotid	Yes	Pruritus	3.07	5,460	109.10	

Note: The table presents clinical data for 20 patients with ELG.

Abbreviations: EBC, Eosinophil Blood Count; IU/mL, International Units per Milliliter. Gender, The patient's gender (M for male, F for female); Age: The patient's age in years; Disease Course (year), The duration of the disease in years; Lesion Site, The anatomical location of the lesion; Lymph Node Involvement: Indicates whether lymph nodes were involved (Yes or No); Clinical Manifestation, Describes the clinical symptoms and manifestations; Peripheral Blood EBC ($x10^9$/L), Eosinophil Blood Count in $x10^9$ per liter of blood; Serum IgE (IU/mL), Serum Immunoglobulin E levels in International Units per milliliter; Lesion Size (cm^3), The size of the lesion in cubic centimeters; Other, Additional notes or observations, such as the presence of urine protein.

medical practice.[3-5] Therefore, the focus of this study is to investigate the effectiveness and safety of low-dose radiotherapy as a potential treatment modality for patients with ELG.

MATERIALS AND METHODS

Study Design

The study included a total of 20 patients with pathologically confirmed Eosinophilic ELG from 2018 to 2022. The research aimed to assess the efficacy of low-dose radiotherapy in ELG patients. The research obtained ethical approval, and all patients provided informed consent. The study strictly adhered to the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Patients with pathologically confirmed ELG; (2) Patients diagnosed within the period from 2018 to 2022; (3) Patients provided informed consent to participate in the study. Exclusion criteria were as follows: (1) Patients not willing to participate in the study; (2) Patients with other severe health issues; (3) Patients with mental health problems.

Patient Characteristics

Patient characteristics encompass a diverse range of demographics, clinical features, and health attributes. (1) Demographics and Gender: Out of the 20 patients, 18 were male, while 2 were female, resulting in a male-to-female ratio of 9:1; (2) Disease Duration: The majority of patients exhibited a protracted illness course, with a median disease duration of 5 years and an average of 6.375 years, ranging from 0.5 to 17 years; (3) Age of Onset: Patients presented with ELG across a broad age spectrum, with onset ranging from 10 to 83 years. Refer to Table 1.

Clinical Presentation and Lesion Characteristics

Lesions were observed in various anatomical locations, including 7 in the cheek, 11 in the parotid gland, 1 in the right upper arm, and 2 in the temporal region. 9 patients were presented with multiple lesions, while 11 patients had solitary lesions. Common clinical manifestations included soft tissue masses without distinct boundaries in 90% of patients, local skin roughness, desquamation with notable pruritus in 80%, and mild pain in 5% of patients.

Treatment History

Only 1 (5%) patient had previously undergone surgical treatment. 12 (60%) patients experienced a recurrence of the condition after initial treatment. The remaining patients had not received any prior treatment.

Laboratory Findings

Normal ranges for peripheral blood eosinophil count and serum Immunoglobulin E (IgE) in our hospital were 0.020-0.520×10^9/L and 0-100 IU/mL, respectively. Prior to treatment, 85% of patients displayed elevated peripheral blood eosinophil counts, and 100% exhibited increased serum IgE levels. Only 1 patient with hypoproteinemia showed elevated urinary protein and D-dimer levels, and another patient presented with anemia. Moreover, 6 patients displayed a spontaneous fluctuation in the size of their lesions during the course of the disease, with lesions occasionally increasing and decreasing in size.

Treatment

All the enrolled patients received low-dose radiotherapy treatment. The treatment protocol is outlined in the following.

Radiotherapy Procedure. The radiotherapy procedure followed a well-defined protocol, with each of the 20 patients

giving their informed consent for both radiotherapy and participation in the clinical study. Patients were positioned in a supine manner and securely immobilized using a foam pad and a head and neck thermoplastic film to ensure precise treatment delivery.

Radiation Target Definition. The CT simulator was utilized to delineate the radiation target area. This target area was categorized into three volumes: (1) Gross Tumor Volume (GTV): encompassing the visible lesion and swelling areas on imaging; (2) Clinical Tumor Volume (CTV): defined as an expansion of the GTV by 3mm outward; and (3) Planning Target Volume (PTV): extending an additional 3mm outward from the CTV.

Radiotherapy Technique. The treatment plan employed three-dimensional conformal intensity modulation radiotherapy using 6MV-X-ray. The radiation dose required to achieve a 95% control rate for the tumors ranged between 30-50 Gy, administered in 2 Gy fractions over 15-25 sessions, five times per week.

Tissue Tolerance. Throughout the treatment, careful consideration was given to the tolerance levels of normal tissues, including the parotid gland and surrounding structures.

Data Analysis

Descriptive statistics were employed to summarize the patient characteristics, treatment parameters, and clinical manifestations. The effectiveness of low-dose radiotherapy in controlling ELG was evaluated by assessing response rates, recurrence rates, and any observed variations in lesion size during the course of the disease. Furthermore, laboratory findings, including peripheral blood eosinophil count and serum IgE levels, were analyzed to assess their relationship with treatment outcomes.

RESULTS

Treatment Responses

Following low-dose radiotherapy, 3 patients (15%) achieved a complete response (CR), indicating the complete disappearance of the lesions. 8 patients (40%) achieved a partial response (PR), signifying a lesion reduction rate of more than 50%. 6 patients (30%) showed stable disease (SD), with a lesion reduction rate of not more than 50%. The total response rate, encompassing CR, PR, and SD, reached 90%.

Radiation-Induced Effects

Notably, 2 patients experienced enlargement of lesions after radiotherapy. However, their peripheral blood eosinophil counts returned to normal levels, and serum IgE levels were reduced by over 40% (48.38% and 40.4%, respectively). Specific radiation doses led to varying skin reactions: patients receiving 30-36 Gy experienced skin pigmentation in the radiation target area (grade I adverse reaction), while those receiving 40 Gy exhibited skin pigmentation and alopecia (grade II adverse reaction).

Follow-up and Long-Term Outcomes

Over a median follow-up period of 23.6 months (ranging from 10.3 to 43 months), lesions within the radiotherapy target area were effectively controlled for all patients without the need for glucocorticoids or additional treatments. Four patients continued to experience occasional pruritus after radiotherapy. One patient experienced recurrence outside the target area 3 years later, with the recurrent lesion located in the groin area. While it presented pruritus symptoms and spontaneous variations in size, it did not necessitate additional treatment. Importantly, no cases reported serious long-term adverse reactions related to radiotherapy during the follow-up period. Refer to Table 2 for an overview of the treatment outcomes.

Table 2. The Curative Effects of Low-Dose Radiotherapy on 20 Patients

Case	Previous Treatment	Radiotherapy Dose	Lesion Size After Treatment (Cm^3)	Peripheral Blood After Treatment		2-Year Follow-Up
				EBC ($\times 10^9$/L)	Serum IgE (IU/mL)	
1	Recurrence	50Gy/25F	168.41	0.6	4,990	No recurrence
2	Untreated	30Gy/15 F	61.08	0.48	1,160	Recurrence(groin),pruritus,
3	Untreated	50Gy/25F	129.96	0.15	1,580	CR, pruritus,
4	Recurrence	30Gy/15F	25.33	0.470	214	PR, pruritus
5	Recurrence	30Gy/15F	17.68	0.520	2,470	No recurrence
6	Recurrence	30Gy/15F	23.24	0.12	7,160	No recurrence
7	Recurrence	40Gy/20F	198.76	0.27	3,750	CR, No recurrence
8	Recurrence	40Gy/20F	12.3	1.950	7,840	CR, No recurrence
9	Untreated	36Gy/18F	50.4	0.44	2,430	PR, No recurrence
10	Untreated	36Gy/18F	203.89	0.190	4,830	PR, No recurrence
11	Postoperative	30Gy/15f	0	0.370	109	No recurrence
12	Recurrence	30Gy/15F	0	0.39	1,720	Pruritus, no recurrence
13	Untreated	30Gy/15F	124.67	0.21	1,000	No recurrence
14	Recurrence	40Gy/20F	189.65	0.36	81.9	CR, No recurrence
15	Recurrence	30Gy/15F	46.37	0.93	30,800	No recurrence
16	Untreated	32Gy/16F	34.32	0.690	770	PR, No recurrence
17	Untreated	30Gy/15F	268.3	0.44	640	No recurrence
18	Untreated	36Gy/18F	77.34	0.29	2,160	No recurrence
19	Untreated	30Gy/15F	0	0.300	1,390	No recurrence
20	Recurrence	50Gy/25F	168.41	0.020	3,250	CR, No recurrence

Abbreviations: EBC, Eosinophil Blood Count (x10^9/L); Serum IgE, Serum Immunoglobulin E (IU/mL); Gy, Gray; F, Fractions; CR, Complete Response; PR, Partial Response.

DISCUSSION

At present, the etiology of ELG remains unclear. This condition is widely acknowledged as a rare, chronic inflammatory disease, a consensus reached through the extensive diagnostic and treatment experiences shared by both Chinese and international scholars.[4-5] Despite its benign nature, ELG exhibits a propensity for recurrence after treatment.[5] During our study, we observed that ELG displays spontaneous fluctuations in response to changes in the patient's immune system, and the likelihood of recurrence appears to be closely associated with the patient's immune status.

Currently, there are no established clinical observation indicators for ELG diagnosis. Additionally, the age range of the 20 patients in our study was quite extensive, with the initial onset age spanning from 10 to 80 years. We considered that the variations in disease control and recurrence might be linked to differences in the immune system related to age. However, prior research has shown no significant correlation between age and various factors, including region, race, complications, diversity, lesion site, lesion size, peripheral blood eosinophil count, serum IgE levels, initial therapy, recurrence, and other clinical outcomes.[3] Therefore, we refrained from conducting a further analysis of the impact of age on the study results.

Typically, patients with ELG face a higher risk of recurrence if they present with specific risk factors. These factors include a lesion diameter exceeding 3 cm, a disease course of more than 5 years, a peripheral blood eosinophil count 1.2 times higher than the upper limit of normal, and serum IgE levels surpassing 10 000 IU/mL. In cases where these high-risk factors are present, the recommended approach is to combine surgery with adjuvant therapy to reduce the risk of recurrence. Notably, ELG is characterized by infiltrating growth and a tendency to invade lymph nodes, rendering complete surgical removal challenging.

Medical interventions, such as steroids or chemotherapy, provide short-term control over ELG but often result in exacerbation upon drug withdrawal. In cases of recurrence and resistance to standard treatments, radiotherapy emerges as a favorable option due to its precise efficacy and non-invasive nature.[5-10] In our study, 90% of patients experienced a reduction in lesion size by over 50% following radiotherapy.

While two patients exhibited lesion enlargement post-treatment, their peripheral blood eosinophil counts returned to normal, and the proportion of serum IgE significantly decreased, surpassing 40% (48.38% and 40.4%, respectively). Only one patient experienced a recurrence outside the target area, specifically in the groin area, three years after radiotherapy. In sum, radiotherapy has demonstrated its effectiveness in controlling ELG and preventing its recurrence.

Regarding the radiotherapy dose, studies have recommended a range of 20-40 Gy over 3 to 4 weeks as an appropriate treatment for ELG. Additionally, some scholars suggest radiation doses exceeding 40 Gy,[12] which might be associated with the associated high-risk factors. In any case, it is important to note that radiotherapy can be discontinued when the lesion decreases by 70% rather than insisting on achieving complete responses.

Considering the findings of this study, it is suggested that the dosage range should be determined based on the pathological analysis of ELG, as reported in previous studies. A past study[14] indicated that a radiation dose of 20-30 Gy could significantly restore capillary endothelium, eliminate eosinophils, and reduce lymphocytes within ELG lesions. However, in our current study, we observed that some patients continued to experience pruritus symptoms despite lesion control and reduced peripheral blood eosinophilic cell count. Past research has suggested that pruritus may be linked to nerve damage resulting from the infiltration of lymphocytes and eosinophils.[15]

When managing benign diseases, our goals extend beyond achieving effective disease control and reducing the risk of recurrence. We must also thoroughly assess the potential long-term effects of radiotherapy on healthy tissues. A study[16] reported that over an average follow-up period of 65 months, ELG patients who received radiotherapy within the range of 20-45 Gy did not develop secondary lesions. In our study, the longest follow-up period extended to 43 months, during which radiotherapy did not induce severe long-term adverse reactions, including secondary lesions.

The findings of this study emphasize the effectiveness of radiotherapy as a treatment option for ELG. A substantial reduction in lesion size was observed in 90% of patients, with minimal recurrence and manageable adverse reactions. Moreover, the study highlights the significance of considering individualized treatment strategies, particularly for patients with high-risk factors, to enhance therapeutic outcomes while minimizing the long-term impact on normal tissues. These results contribute to a growing body of evidence supporting radiotherapy as a valuable approach for ELG management, providing both disease control and patient comfort.

Study Limitations

This study presents valuable insights into the efficacy of radiotherapy for ELG. However it is important to acknowledge its limitations. First, the sample size was relatively small, potentially limiting the generalizability of the findings. Second, the study's duration may not capture long-term effects or rare adverse reactions associated with radiotherapy. Additionally, the absence of a control group makes it challenging to compare the outcomes directly. Lastly, this study primarily focuses on short-term responses and does not provide extended follow-up data. Despite these limitations, the results contribute to the understanding of ELG treatment, and future research with larger cohorts and longer follow-up periods can further enhance our knowledge of this condition and its management.

CONCLUSION

In summary, this study concludes that radiotherapy emerges as a safe, non-invasive, and effective treatment for patients with recurrent and refractory ELG. The recommended radiation dose falls within the range of 20-40 Gy, facilitating a substantial reduction in ELG recurrence. However, it is crucial to acknowledge that the current study's follow-up duration might not suffice for a comprehensive assessment of long-term adverse reactions. Therefore, extended follow-up periods are warranted to provide a more thorough evaluation and validation of these findings, especially considering the benign nature of the disease.

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CONFLICT OF INTERESTS
The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS
The data supporting the findings of this study are available from the corresponding author upon request, subject to reasonable conditions.

AUTHORS' CONTRIBUTIONS
YY, HZ and YS designed the study and performed the experiments; XL, WZ and YX collected the data; YD, ZL and CN analyzed the data; YY, HZ and YS prepared the manuscript. All authors read and approved the final manuscript. YY and HZ contributed equally to this work.

ETHICAL COMPLIANCE
This study was approved by the ethics committee of Affiliated Hospital of Inner Mongolia Medical University. Signed written informed consent was obtained from the patients and/or guardians.

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