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ORIGINAL ARTICLE

Expression and Significance of Inflammatory Factors in Idiopathic Spinal Epidural Lipomatosis (Grade III)

Mingkun YANG[1*], Hang ZHANG[1*], Minyi LIU[1*], Xindong JIA[1*], Tao DU[1], Dengpu WU[1]

1 Department of Spinal Surgery, Central Hospital of Bazhong City, Bazhong, Sichuan Province 636000, China.
*Mingkun Yang, Hang Zhang, Minyi Liu, Xindong Jia are co-first authors.

Correspondence to: Mingkun Yang, MD
Department of Spinal Surgery, Central Hospital of Bazhong City,
No. 1 Nanchi Street, Bazhong, Sichuan Province 636000, China
TEL: -86-18398207677, E-MAIL: ymkun1121@163.com

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Abstract

BACKGROUND: Idiopathic spinal epidural lipomatosis (iSEL) is frequently associated with the utilization of steroids, endocrine disorders, obesity, and surgical interventions. Nevertheless, the pathogenesis of iSEL remains inadequately understood. The study aimed to investigate the contribution of inflammatory factors to idiopathic epidural lipomatosis.

METHODS: Thirteen patients with iSEL (Grade III, iSEL group) and 12 patients with lumbar disc herniation (control group) who underwent unilateral biportal endoscopy from March 2020 to April 2023 were enrolled. Histological examination of adipose tissue was the performed to analyze expressions of pro-inflammatory cytokines (TNF-α, IL-1β), and anti-inflammatory factors (arginase-1, IL-10) in serum and epidural adipose cells.

RESULTS: Compared with the control group, the number of inflammatory cell infiltrations per field in HE-stained sections was significantly elevated, TNF-α and IL-1β expression in adipocytes of epidural adipose tissue were markedly higher, and arginase-1 and IL-10 expression were significantly lower in the iSEL group (all $p < 0.001$). However, no statistically significant differences were observed in the serum level of TNF-α, IL-1β, arginase-1, and IL-10 between the two groups ($p = 0.963$). In addition, there was also no significant disparity in adipocyte size between the two groups ($p = 0.739$).

CONCLUSION: iSEL demonstrated elevated inflammatory cells and imbalance towards proinflammatory cytokines in adipocytes of epidural adipose tissue that may be associated with the pathogenesis of symptomatic iSEL. These data suggest that inflammatory response could be one of the mechanisms of iSEL. However, further multicenter epidemiological investigations and rigorous basic and clinical research are warranted to elucidate the specific etiology of iSEL.

BACKGROUND

Spinal Epidural Lipomatosis (SEL) is a rare pathological condition characterized by the anomalous deposition of adipose tissue outside the dura mater within the spinal canal (Kim *et al.* 2019; Mallard *et al.* 2021). Clinical manifestations of SEL encompass a range of symptoms, such as radiculopathy, myelopathy, gait disturbance, cauda equina syndrome, and paralysis (Louachama *et al.* 2021). The incidence of SEL ranges from 2.5%

to 25% and is more commonly observed in middle-aged and elderly individuals. It exhibits a higher prevalence in males than females and predominantly affects the lumbar spine, followed by the thoracic spine. SEL at the cervical spine level is extremely rare (Kim & Mendelis 2019; Walker *et al.* 2021; Larose *et al.* 2019). The etiological factors associated with SEL involve long-term administration of steroids, endocrine disorders, obesity, and surgical procedures (D'Agostino *et al.* 2023). While the exact mechanism of SEL remains unclear, it is widely believed to be associated with metabolic syndrome (D'Agostino *et al.* 2023). However, it has been reported that approximately 17% of SEL cases are not linked to these factors, leading to the classification of such cases as iSEL (Fogel *et al.* 2005; Eap *et al.* 2010; Sato *et al.* 1995).

Since 1982, there have been documented cases of iSEL in the medical literature (Badami & Hinck 1982). Haddad *et al.* (1991) suggested that SEL should be recognized as a condition that primarily affects obese patients, where the key mechanism involves excessive growth of epidural fat, leading to compression of the spinal cord and nerves. However, instances of SEL have also been observed in non-obese individuals, indicating that iSEL may involve additional pathogenic mechanisms (Stern *et al.* 1994). Based on the available literature, it is imperative to exclude factors such as a history of steroid use, endocrine disorders, obesity, and surgical interventions when diagnosing the iSEL (D'Agostino *et al.* 2023; Miyakoshi *et al.* 2003).

Currently, there is a scarcity of case reports and limited information regarding the etiology of iSEL. Typically, the size of adipocytes is related to the extent of obesity, as obese individuals tend to have enlarged adipocytes due to increased triglyceride deposition. Previous studies have demonstrated that enlarged adipocytes express pro-inflammatory cytokines and the expressions of tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) are positively correlated with the degree of human obesity (Hotamisligil *et al.* 1993; Dandona *et al.* 1998).

In 2016, Fujita *et al.* (2016) reported a causal relationship between inflammatory factors, specifically TNF-α and IL-1β, in the epidural adipose tissue of obese patients with SEL. However, it remains unclear whether these inflammatory factors are also aberrantly expressed in the adipocytes of epidural adipose tissue in non-obese patients with iSEL, as there is a lack of relevant reports addressing this aspect. Inflammatory factors, which generally include pro-inflammatory factors (TNF-α, IL-1β) and anti-inflammatory factors (Arginase-1, IL-10), were hypothesized to have been involved in the pathogenesis of non-obese patients with iSEL. Therefore, in this study, we collected epidural fat tissues from non-obese patients with iSEL and patients with lumbar disc herniation for morphological analysis, analyzed the characteristics of epidural fat tissue in patients with iSEL and intraspinal fat tissue in patients with lumbar disc herniation, and investigate the contribution of inflammatory factors to idiopathic epidural lipomatosis.

MATERIALS AND METHODS

Study Subjects

In this study, a comparative analysis was performed based on the clinical data of thirteen patients with symptomatic iSEL (Grade III (Ishikawa *et al.* 2006)), who underwent unilateral biportal endoscopy (UBE) surgery between March 2020 and April 2023, along with twelve patients who underwent UBE surgery for lumbar disc herniation. The specific surgical technique was performed according to the method described in reference (Kang *et al.* 2019). Ethical approval for this study was obtained from our hospital's ethics committee (approval number: 20200016), and written informed consent was obtained from all participating patients.

Diagnostic criteria for patients with iSEL were as follows. (1) The clinical history and physical examination were consistent with the affected spinal segment, presenting symptoms such as recurrent lumbar back pain, intermittent claudication, radiating leg pain,

Tab. 1. Clinical data of the two groups of patients

	iSEL group	Control group	*p*
Number of cases	13	12	-
Gender (male/female)	7/6	6/6	0.76
Age (± years old)	48.5 ± 2.5	46.5 ± 4.6	0.69
BMI	22.4 ± 1.3	22.0 ± 1.6	0.75
COD (years)	3.2 ± 0.6	3.1 ± 0.5	0.81
Expression of serum TNF-α (pg/mL)	9.5 ± 3.7	9.3 ± 3.1	0.77
Serum IL-1β expression (pg/mL)	11.2 ± 4.6	11.6 ± 3.5	0.86
Serum Arginase-1 expression (ng/mL)	5.1 ± 2.3	5.6 ± 1.9	0.75
Serum IL-10 expression (pg/mL)	2.4 ± 0.8	2.2 ± 0.5	0.84

iSEL indicates idiopathic spinal epidural lipomatosis; BMI indicates body mass index; COD indicates course of disease

weakness, sensory abnormalities, and possible cauda equina syndrome. (2) Magnetic resonance imaging (MRI) revealed epidural fat thickness greater than 7 mm at the affected spinal segment. (3) Epidural fat thickness accounting for more than 50% of the diameter of spinal canal. (4) Body mass index (BMI) was less than 27.5 kg/m^2. (5) No (Patients without the) history of long-term hormone use or related endocrinal metabolic diseases. (6) No (Patients without the) history of spine surgery.

On the other hand, diagnostic criteria for patients with lumbar disc herniation were as follows. (1) The patient was over 18 years. (2) The clinical history and physical examination showed the consistent affected spinal segment, exhibiting symptoms such as recurrent lumbar back pain, intermittent claudication, radiating leg pain, weakness, sensory abnormalities, and possible cauda equina syndrome. (3) MRI confirmed the diagnosis of lumbar disc herniation. (4) Patients underwent standardized conservative treatment for more than 3 months (without symptom relief and with progressive spinal cord and nerve symptoms). (5) BMI was less than 27.5 kg/m^2. (6) Patient had no contraindications for spinal endoscopic surgery.

Research Methods and Main Observation Indicators

The patients were divided into two groups for the study. The iSEL group consisted of 13 patients (7 males and 6 females) with iSEL (Grade III) who underwent UBE surgery. In contrast, the control group included 12 patients (6 males and 6 females) with lumbar disc herniation who underwent UBE surgery.

The main observational indicators included the BMI, course

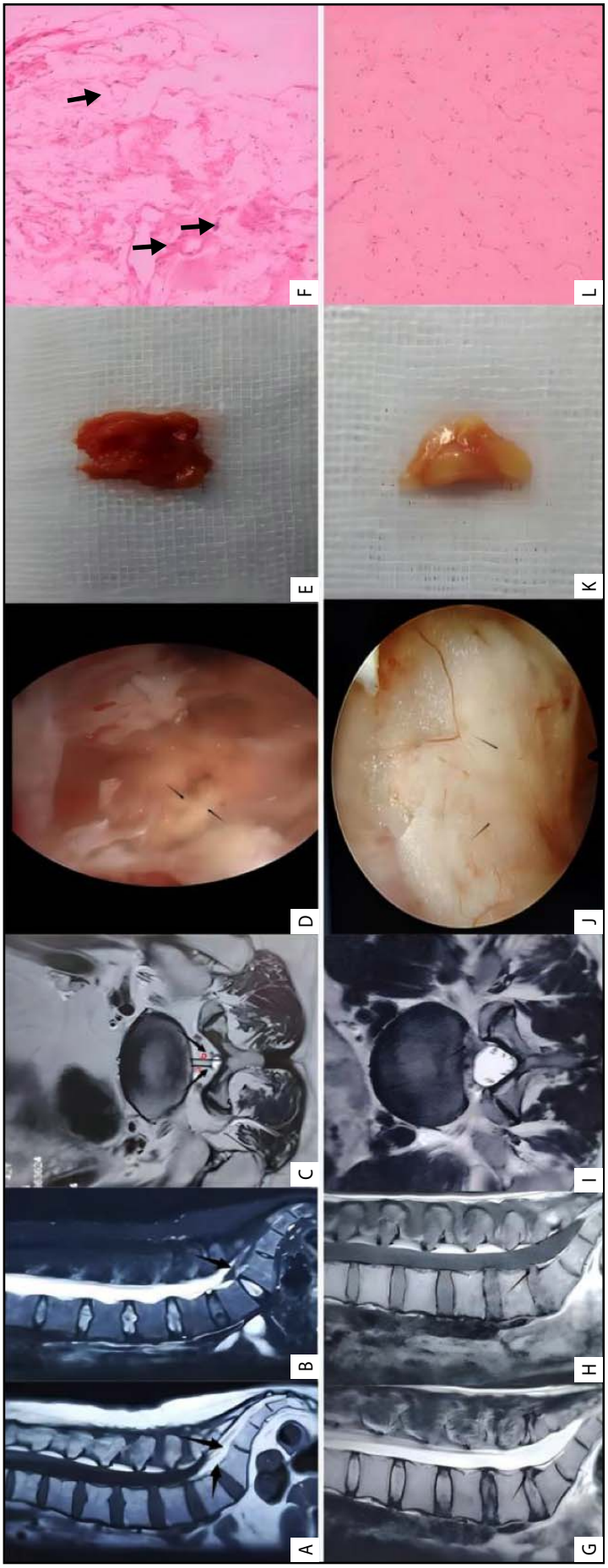

Fig. 1. A, B, C: the preoperative MRI data of patients with idiopathic spinal epidural lipomatosis (iSEL), T1-weighted images can clearly distinguish the epidural adipose tissue from other vertebral canal contents (shown by arrows). **D:** is the microscopic observation of a significant increase of adipose tissue in the vertebral canal, adipose tissue without envelope, obvious vascular hyperplasia in the tissue, and no pulsation with the dura. **E:** the excision of adipose tissue, containing more vascular tissue. **F:** the microscopic observation of fibers, blood vessels, and adipose tissue in patients with iSEL, showing large inflammatory cell infiltration. **G, H, and I:** preoperative MRI data of patients with lumbar disc herniation and the herniated tissue is disc tissue (shown by arrows). **J:** displays the microscopic observation of adipose tissue in the spinal canal, which exhibits a sparse, semi-fluid pattern (shown by arrows) and can pulsate significantly with the dura. **K:** is part of the excised adipose tissue without abnormal manifestations. **L:** displays the HE staining analysis (X100) of adipose tissue in a patient with lumbar disc herniation with no abnormal adipose tissue particles and no obvious inflammatory cell infiltration.

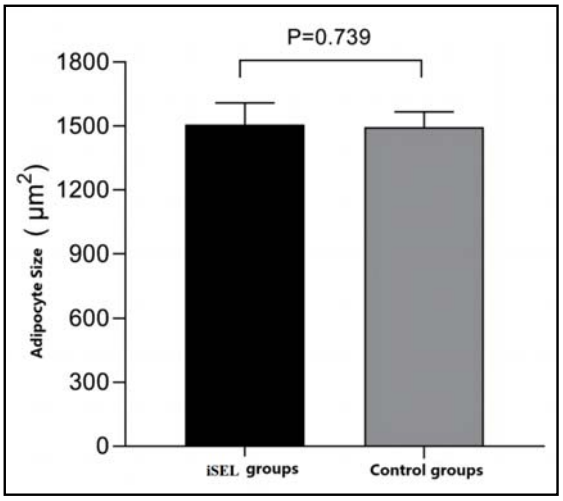

Fig. 2. Comparison of adipocyte size in patients between the two groups.

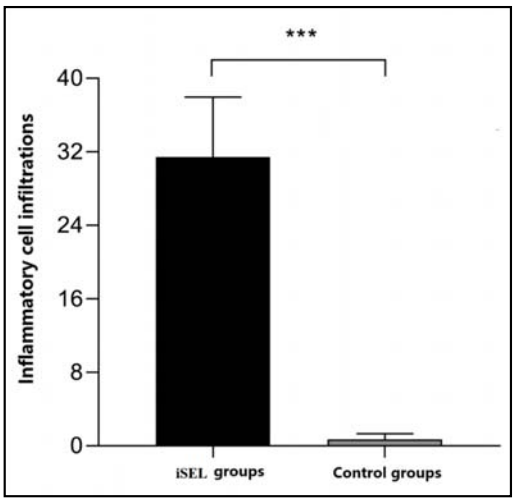

Fig. 3. Comparison of the number of adipose tissue inflammatory cell infiltrates (per field of view) between the two groups ($p < 0.001$).

of disease, histology (adipocyte size and number of infiltrating inflammatory cells) of patients in the two groups. Additionally, expressions of TNF-α, IL-1β, Arginase-1, and IL-10 were detected in the serum and epidural adipose tissue adipocytes of the two groups.

The ELISA detection method was employed. After the collection of blood (or adipose tissue homogenate treated with PBS as the homogenization medium), the samples were centrifuged at 3,000 rpm for 10 minutes, the resulting supernatant was stored at -20°C for later use. Prior to the measurement, the samples were brought to room temperature, and the ELISA measurements were conducted according to instructions provided in the ELISA kit (DIACLONE, France).

Statistical Analysis

The data were performed statistically analyzed using SPSS 26.0 (SPSS, United States). Independent sample t-tests were employed to compare continuous data between the two groups, assuming normal distribution and homogeneity of variances. The results were presented as mean ± standard deviation. A two-sided test was used, and $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 displays the demographic characteristics of the patients in the observation and control groups. The mean age of the iSEL group was 48.5 ± 2.5 years, while that in the control group was 46.5 ± 4.6 years. Statistical analysis revealed no statistically significant differences between the two groups in terms of gender ratio, age, BMI, and disease duration ($p > 0.5$).

Histological comparison of the spinal epidural adipose tissue between the two groups was summarized as follows. Under intraoperative microscopy, the iSEL group exhibited a significant increase in intraspinal adipose tissue, characterized by the absence of a capsule, notable neovascularization within the tissue. The adipose tissue did not demonstrate pulsation with the dura mater. Conversely, the control group displayed sparse, semi-fluid adipose tissue within the spinal canal, which exhibited pulsation with the dura mater. The excised adipose tissue from the iSEL group had presented significant neovascularization compared to that from the control group, as illustrated in Figure 1. HE staining analysis revealed no significant difference in adipocyte size between the iSEL group and the control group (1507.29±101.54 μm² vs. 1493.75±72.51 μm²; t=0.339, p=0.739), as illustrated in Figure 2. The number of infiltrating inflammatory cells per field of view was significantly higher in the iSEL groups (31.43 ± 6.53 vs. 0.67 ± 0.65; t=16.527, $p < 0.001$), as illustrated in Figure 3.

The expressions of TNF-α, IL-1β, Arginase-1, and IL-10 in serum in two groups showed no statistically significant differences (t = 0.215, p = 0.942), as shown in Table 1. However, the expressions of TNF-α and IL-1β in the spinal epidural adipose tissue were significantly higher in the iSEL group ($p < 0.001$). Conversely, the expressions of Arginase-1 and IL-10 in the spinal epidural adipose tissue were significantly lower in the iSEL group compared to the control group ($p < 0.001$). The graphical representations of the results were given in Figures 4–7.

DISCUSSION

Currently, relatively few studies have been conducted on SEL, in which the definition of nonspecific SEL is somewhat controversial. Some studies suggest that the etiology of SEL includes long-term administration of exogenous corticosteroids, conditions leading to increased endogenous corticosteroids, obesity, surgery, and even non-alcoholic fatty liver disease, and human immunodeficiency virus antiviral therapy, (Kim & Mendelis 2019; Abe *et al.* 2019; Billings & Hoyt, 2012;

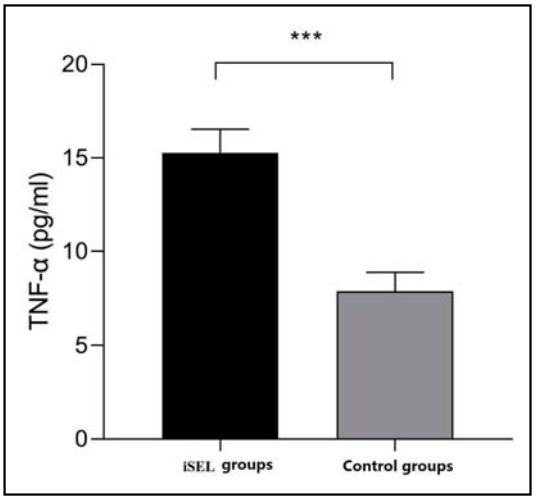

Fig. 4. Comparison of expression of TNF-α in adipocytes ($p < 0.001$).

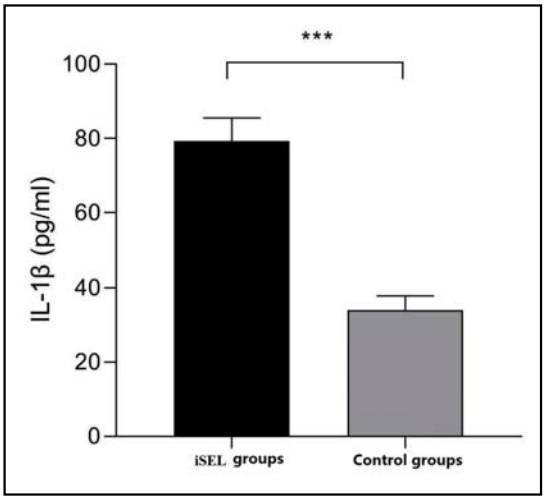

Fig. 5. Comparison of expression of IL-1β in adipocytes ($p < 0.001$).

Vince *et al.* 2005; Cersósimo *et al.* 2002; Ebright *et al.* 2001). However, there are cases of SEL where none of these known causes are present. These cases are referred to as iSEL and account for approximately 17% of all patients with SEL (Eap *et al.* 2010; López-González & Resurrección Giner 2008). Although a previous study (Fujita *et al.* 2016) reported 16 cases of iSEL, all of those patients were obese, with 5 of them having a BMI greater than 30. These patients should be categorized as cases of SEL with obesity rather than iSEL. This study focuses on iSEL and meticulously excluded factors such as a history of corticosteroid use, endocrine disorders, obesity, and previous surgeries in the selected cases. Preoperative assessments also ruled out conditions such as fatty liver and human immunodeficiency virus infection. Therefore, these cases align more closely with the diagnosis of iSEL. Furthermore, the incidence of iSEL may vary across different ethnicities, with a reported high incidence rate of 68.8% in the Korean population (Yoo *et al.* 2014), while Western countries exhibit an incidence rate of 17% (Fogel *et al.* 2005). However, these reports did not specifically exclude obese patients, suggesting that the incidence of iSEL should be lower than the aforementioned rates.

In this study, all thirteen cases occurred in the lumbar spine, which suggests that the lumbar spine is the most common site for iSEL. The lumbar spine is particularly susceptible to SEL due to its larger osseous spinal canal, which allows for greater deposition of adipose tissue (Larose *et al.* 2019). Comparing the epidural adipose tissue between two group revealed a significant increase in epidural adipose tissue in patients with iSEL. Meanwhile, there was no significant enlargement of adipocytes, which distinguishes the patients with iSEL from those with of SEL with obesity (Fujita *et al.* 2016). However, both microscopic and macroscopic observations revealed distinct characteristics of the adipose tissue in patients with iSEL. It exhibited significant neovascularization, lack of pulsation with the dura mater, and prominent infiltration of inflammatory cells. These features deviated from the cohesive and semi-fluid nature of normal epidural adipose tissue and resulted in the impairment of its normal physiological function for spinal cord nerves. This suggests that the adipocytes within the epidural adipose tissue of patients with iSEL exhibit pathological changes. Through the measurement of expression of TNF-α, IL-1β, Arginase-1, and IL-10 in the epidural adipocytes of patients, it was observed that the expressions of TNF-α and IL-1β were significantly higher while those of Arginase-1 and IL-10 were significantly lower in the iSEL group. This suggests that inflammatory reactions are the primary manifestation of diseased adipocytes in patients with iSEL. Moreover, the observed lower levels of factors suggest a decreased inhibition of inflammation compared to normal levels. These results indicate that symptomatic iSEL may be associated with local inflammatory reactions occurring in local adipocytes. In addition, there was no significant difference in the relevant cytokines of serum between the two groups, which may be due to the isolation between the spinal canal and the circulatory system, resulting in inflammation limited to local adipose tissue. This also suggests that blood tests are difficult to provide diagnostic clues for iSEL.

The exact mechanism underlying SEL remains incompletely understood. Jaafar *et al.* (2021) suggested a potential causal relationship between chronic inflammation and the development of epidural lipoatrophy. We speculate that when the lumbar spine develops an inflammatory response due to injury, it may stimulate the proliferation of localized tissues, such as epidural adipose tissue; on the other hand, when localized adipose tissue develops a pathologic hyperplasia due to some reasons, it is itself accompanied by the development of some inflammatory response. Some studies have also found a strong association between metabolic syndrome and SEL, in which hypertension and

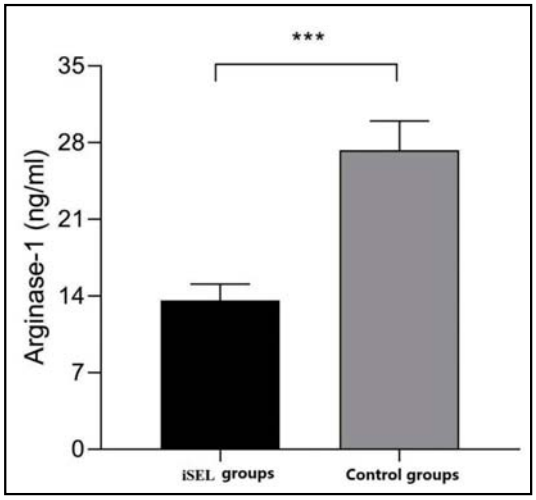

Fig. 6. Comparison of expression of Arginase-1 in adipocytes ($p < 0.001$).

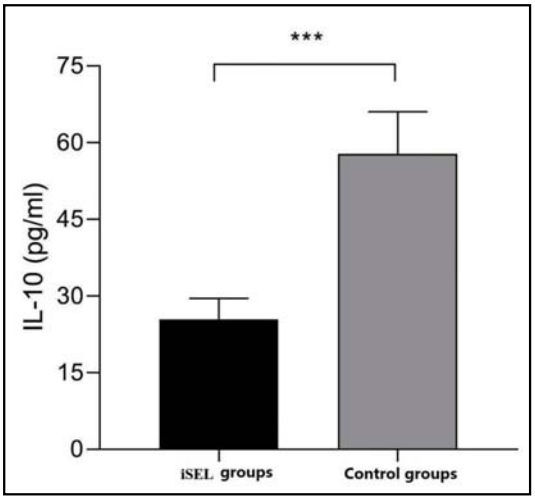

Fig. 7. Comparison of expression of IL-10 in adipocytes ($p < 0.001$).

visceral fat area were independently associated with SEL (Ishihara *et al.* 2019). However, this study mainly studied patients with metabolic syndrome, which is not a part of iSEL, so the differences in hypertension and visceral fat area between the two groups were not compared in our study. However, regardless of the cause, the primary manifestation involves excessive growth of epidural adipose tissue, which gives rise to corresponding clinical symptoms (Fogel *et al.* 2005; Mallard *et al.* 2021; Yasuda *et al.* 2018). The increased adipose tissue can exert mass effect or cause venous congestion within the spinal canal, resulting in compression of the affected spinal cord segment or nerve roots and causing clinical symptoms resembling those of degenerative lumbar disorders (López-González and Resurrección Giner 2008; Quint *et al.* 1988; Papastefan *et al.* 2018).

The diagnosis of SEL currently relies on a comprehensive evaluation of medical history, physical examination findings, and imaging techniques such as CT and MRI. The characteristic feature of SEL is the abnormal increase of epidural adipose tissue, most commonly observed at the L5-S1 level of the lumbar sacral spine. Among the available imaging modalities, MRI provides the most accurate representation of adipose tissue, while CT can help assess signs of nerve root compression and spinal stenosis. The severity of SEL typically determined by grading the epidural adipose tissue on MRI scans (Ishikawa *et al.* 2006). Following these criteria, this study classified all thirteen patients as SEL grade III, which was consistent with their clinical symptoms and the findings observed on their MRI scans.

Treatment approaches for SEL vary depending on the underlying causes (Kim *et al.* 2019; D'Agostino *et al.* 2023). Initially, conservative treatment methods are typically attempted; however, studies have shown that approximately 90% of patients eventually require surgical intervention (Kim *et al.* 2019). For patients who do not respond to conservative treatment and experience worsening symptoms, decompression or laminectomy surgery is often necessary. The surgical outcomes are influenced by the underlying cause of SEL and the specific spinal segment affected (Kim *et al.* 2019; Fujita *et al.* 2016; Kellett *et al.* 2016). In this work, the UBE surgery was performed on patients with symptomatic iSEL, and the postoperative results were favorable, with the resolution of lower limb pain symptoms and no surgical complications. This indicates that surgical decompression is a viable treatment option for patients with symptomatic iSEL.

CONCLUSION

Our findings revealed that patients with iSEL exhibited a significant increase in epidural fat tissue along with pathological features such as denser adipose tissue (characterized by non-dispersed and semi-fluid characteristics), insufficient pulsation with the dura mater, and prominent neovascularization within the tissue. Moreover, there was a significant elevation in expressions of TNF-α and IL-1β in adipocytes, while expressions of Arginase-1 and IL-10 were decreased. These results suggest that the pathogenesis of symptomatic iSEL may be associated with an inflammatory response in local adipocytes. However, given the low incidence of iSEL and the limited number of cases included in this study, further multicenter epidemiological investigations and rigorous basic and clinical research are warranted to elucidate the specific etiology of iSEL.

DECLARATIONS

Ethics approval: The study was approved by the Ethics Committee of Central Hospital of Bazhong City (approval number: 20200016). Written informed consent was obtained from all patients.
Consent for publication: Not applicable.

Availability of data and materials: The data of this study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: MY drafted the manuscript, and was involved in conception and design, acquisition, analysis and interpretation of data. HZ, ML, XJ, TD, DW were involved in the acquisition and interpretation of data. All authors read and approved the final manuscript.

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