Subcutaneous fluid collection: An imaging marker for treatment response of infectious thoracolumbar spondylodiscitis

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HIGHLIGHTS

1. No imaging marker for treatment response of spondylodiscitis (SD) has been proposed.

2. Volume changes of subcutaneous fluid collection (SFC) had significant correlation with changes of C-reactive protein (CRP).

3. SFC can be used as an imaging marker for treatment response of SD on magnetic resonance imaging (MRI).

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ABSTRACT

Purpose: To evaluate prevalence of subcutaneous fluid collection (SFC) in infectious thoracolumbar spondylodiscitis (SD) compared with control patients and to investigate correlation between volume changes of SFC and treatment response of SD.

Materials and methods: This retrospective study was approved by our institutional review board. From April 2011 to March 2012, 49 patients (24 SD and 25 non-SD patients) were enrolled. Prevalence of SFC was evaluated respectively for SD and non-SD patients using magnetic resonance imaging (MRI) on the sagittal short tau inversion recovery (STIR) imaging or fat-saturated T2-weighted imaging (T2WI), and compared. In SD patients with SFC, correlation was investigated between SFC volume on the 1st MRI and initial clinical status. The same analysis was conducted also for SFC volume changes from the 1st to 2nd or last MRI.

Results: SFC was found in 20 patients with SD (83.3%) and 3 non-SD patients (12%) with significant difference ($p< .001$). In 20 SD patients with SFC, 17 patients had follow-up MRI. For the 1st MRI, no significant correlation was found between volume of SFC and initial status of patients, including body weight, body mass index (BMI), white blood cell (WBC), and erythrocyte sedimentation rate (ESR). However, significant positive correlations were found between changes of C-reactive protein (CRP) and SFC

volume from the 1st to 2nd as well as from the 1st to the last MRI (each $p < .05$).

Conclusion: SD patients had significantly higher prevalence of SFC than non-SD patients. Volume changes of SFC had significant correlation with changes of CRP, which can be used as an imaging marker for treatment response of SD on MRI.

Keywords: spondylodiscitis, vertebral osteomyelitis, subcutaneous fluid collection, C-reactive protein, magnetic resonance imaging, short tau inversion recovery.

Abbreviations: ANOVA, analysis of variance; BI, Barthel Index; BMI, body mass index; BW, body weight; CRP, C-reactive protein; DICOM, digital imaging and communication in medicine; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; FIM, Functional Independence Measure; ICC, intra-class correlation coefficient; MRI, magnetic resonance imaging; ROI, region of interest; SD, spondylodiscitis; SFC, subcutaneous fluid collection; STIR, short tau inversion recovery; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; WBC, white blood cell

1. Introduction

Infectious spondylodiscitis (SD) is an infection of the vertebral body and the adjacent intervertebral disc. Annual incidence of SD was estimated between 1:42,000 and 450,000 cases [1] and is currently increasing because of increase in elderly population with diabetes mellitus (DM) and immunocompromised status [2]. Magnetic resonance imaging) is highly sensitive for detecting SD [3]; however, it is not predictive of the treatment response, because high signal intensity of the vertebral body and the adjacent intervertebral disc space on T2-weighted imaging (T2WI) or short tau inversion recovery (STIR) imaging remains even after clinical improvement [4, 5]. For observation of therapeutic response of SD, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are superior to other biological data such as white blood cell (WBC) [5-7], although ESR is affected by many factors[8]. No imaging marker has been proposed for this purpose.

In MRI, subcutaneous fluid collection (SFC) is an occasional finding seen at the deep layer of subcutaneous adipose tissue of the back [9], and it has been reported to be associated with increasing weight in patients with degenerative disc disease or radiculopathy [10]. In our clinical experience, SFC is more commonly seen in patients with SD when compared with patients without SD. However, to our knowledge, its clinical significance has not been investigated.

In this study, we retrospectively analyzed prevalence of SFC in patients who underwent thoracolumbar MRI for SD and non-SD conditions, and investigated clinical significance of SFC in SD patients, specifically relationship between SFC volume and clinical status including blood data, so as to examine if SFC could be an imaging predictor for treatment response or outcome in patients with SD.

2. Materials and methods

This study was approved by the institutional review board, and informed consent was waived due to retrospective nature of this study.

2.1. Patients with infectious spondylodiscitis (Table 1)

Patients clinically suspected of infectious thoracolumbar SD were searched from April 2011 to March 2012, and 30 patients who underwent MRI with clinical diagnosis of SD were found. Patients who had a prior thoracolumbar surgery, bone tumor, acute compression fracture without osteomyelitis, and paraspinal or cutaneous disorders were excluded from this study.

The diagnosis of infectious SD was made by the following criteria: (i) clinical features such as fever and back pain and (ii) MRI findings corresponding to diagnosis of

SD (see 2.5. *Image analysis*). These criteria were applied to the patients clinically suspected of infectious thoracolumbar SD. Bacteriological cultures of blood, disc or soft tissue mass such as paravertebral and psoas abscess were also examined, but positive proof was not considered mandatory due to imperfect sensitivity. Microorganisms were found at the specimen obtained from local lesions of infected disc or abscesses of soft-tissue such as psoas muscle in 7 patients (29%). Blood culture was taken from all but one patient, and 14 patients (58.3%) were positive. Two patients were positive for *mycobacterium tuberculosis* from sputum culture with pathological finding consistent with *mycobacterium tuberculosis* from disc and bone marrow samples (Table 2). There was positive overlap of cultures from local lesion and blood in 4 cases.

Of 30 patients, five patients were not considered SD and one patient was excluded due to complete bedridden condition caused by a traffic accident. Finally, 24 patients (13 males and 11 females; mean age 74.6 years old, ranged from 59 to 89 years old) were included as SD patients in this study.

2.2. Control patients

Non-SD patients were searched in the reporting system from April 2011 until the day when equal or more number of SD patients who measured body weight (BW) and

body mass index (BMI) were found, and 25 control patients (11 males and 14 females; mean 65.6 years old, ranged from 28 to 95 years old) were enrolled. They were almost normal except having spondyloradiculopathy findings. No finding of a prior thoracolumbar surgery, bone tumor, acute compression fracture, osteomyelitis, discitis, and paraspinal or cutaneous disorders was observed.

2.3. Clinical data

The following data were collected in each SD patient at the initial medical examination: (i) BW and BMI, (ii) symptoms (fever, back pain, difficulty in walking, etc.), (iii) initial mobility status (walk, on wheelchair or bed ridden), (iv) comorbidity of DM and immunocompromised status, (v) antibiotic treatment before 1st MRI, (vi) blood data (WBC, CRP and ESR), and (vii) bacteriological data. Blood data on the day nearest to follow-up MR examinations were also collected if available, noting intervals from the first blood test (WBC, 1.4 ± 2.8 days; CRP, 1.3 ± 2.7 days; ESR, 2.8 ± 3.6 days). The Barthel Index (BI) score that measures the patient's performance in 10 activities of daily life [11] and the Functional Independence Measure (FIM) motor score that evaluate 18 items [12] on the day nearest (within 15 days) to initial and follow-up MR examinations were collected, when available. Data on BW and BMI of the control patients were also

collected.

2.4. MRI

MRI studies were performed using 1.5T scanners (Magnetom Avanto and Vision, Siemens Medical Systems, Erlangen, Germany) with the following sequences: sagittal T1-weighted imaging (T1WI; TR/TE, 400-800ms/8-12ms; slice thickness, 4 mm; inter-slice gap, 1 mm; field-of-view, 280×280 mm; matrix size 256×256), sagittal T2-weighted imaging (T2WI; TR/TE, 3635-4604ms/95-120ms; slice thickness, 4 mm; inter-slice gap, 1 mm; field-of-view, 280×280 mm; matrix size 384-512×384-512), and sagittal STIR imaging (TR/TE, 4790/110; inversion time, 130 milliseconds; slice thickness, 4 mm; inter-slice gap, 1 mm; field-of-view, 300×300 mm; matrix size 320-384×320-384) or sagittal fat-saturated T2WI (TR/TE, 4590/60; slice thickness, 4 mm; inter-slice gap, 1 mm; field-of-view, 300×300 mm; matrix size 384-512×384-512). Also conducted was axial T2WI (TR/TE, 4362-4604ms/95-120ms; slice thickness, 4 mm; inter-slice gap, 1 mm; field-of-view, 180×180 mm; matrix size 384-512×384-512).

2.5. Image Analysis

All images were evaluated by a single radiologist (T.K. with experience in

diagnostic imaging for 9 years). Spondylitis (i.e. vertebral osteomyelitis) was defined as presence of hypointensity on T1WI and hyperintensity on STIR or fat-saturated T2WI within the vertebral bone marrow [13, 14]. Discitis was defined as presence of hyperintensity within the intervertebral disc on STIR or fat-saturated T2WI [14]. SD was defined as presence of discitis and osteomyelitis above and below of the affected disc [15]. Clinical symptoms and blood data were also taken into consideration for diagnosis of SD. Epidural, paravertebral and psoas abscess were focal hypointensity on T1WI and fluid-equivalent signal intensity on T2WI, fat-saturated T2WI or STIR imaging [13, 16].

SFC was defined as fluid-equivalent signal intensity located at the deep layer of subcutaneous adipose tissue that consists of two layers (i.e. superficial and deep layers) [9]. Volume measurement of SFC was conducted on the sagittal fat-saturated T2WI or STIR images using a digital imaging and communication in medicine (DICOM) viewer (OsiriX, ver. 5.7.1; http://www.osirix-viewer.com/Downloads.html). Region of interest (ROI) was semi-automatically selected using region growing method of high signal intensity area on STIR or fat-saturated T2WI. SFC volumes on follow-up MRI were also measured, and imaging intervals were noted. The measurements were conducted twice as separate sessions, and the paired measurement values were averaged for further analysis [17]. Other infectious lesions such as epidural, paravertebral, and psoas abscess were also examined

and noted.

2.6. Statistical Analysis

Positive rates of SFC were calculated separately for SD and non-SD patients, and difference was examined using Fisher's exact test. For SFC volume measurements, intra-observer variability was evaluated using intra-class correlation coefficient (ICC) of SFC volume measurements on the 1st to 5th MRI [18]. In SD patients, relations between presence of SFC and initial status (walk, on wheelchair or bedridden) were analyzed using analysis of variance (ANOVA). Correlational analysis was conducted between SFC volumes on the 1st MRI and corresponding scores of BI, FIM motor, BW, BMI and blood data. SFC volume changes from the 1st to 2nd or last MRI were also analyzed. Differences in SFC frequency by abovementioned comorbid conditions were examined using Mann-Whitney U tests. A *p* value less than .05 was considered statistically significant. Statistical analysis was conducted with a commercially available statistical software package (MedCalc version 13.1.2; MedCalc Software, Ostend, Belgium).

3. Results

3.1. Prevalence of SFC in SD and non-SD patients

Twenty SD patients (9 males and 11 females) showed SFC on the 1st MRI (83.3%), whereas 3 non-SD patients (1 male and 2 females) showed SFC (12.0 %), and the difference was statistically significant ($P < .001$). Mean BW and BMI of 25 non-SD patients were 54.6 ± 12.2 kg and 21.3 ± 3.4 kg/m^2, respectively. Those of 24 SD patients were 57.8 ± 18.6 kg and 23.2 ± 7.0 kg/m^2, and no statistically significant difference was observed.

3.2. Correlation of clinical symptoms and blood data with SFC volume in SD patients

Initial symptoms were back pain ($n = 9$), fever ($n = 5$), back pain & fever ($n = 8$), and others ($n = 2$). Initial status of patients was divided into three groups: walk ($n = 6$), on wheelchair ($n = 2$) or bedridden ($n = 16$). Patients had one or more comorbid conditions: DM ($n = 10$), chronic renal disease ($n = 5$) and chronic liver disease ($n = 5$). There were prednisolone users ($n = 4$). Fifteen patients were given antibiotics before initial MRI (14 patients with intravenous antibiotics and 1 patient with oral antibiotics). Mean WBC, CRP and ESR in each time were shown in supplementary Table 1. No significant correlation was found between volume of SFC on the 1st MRI and clinical symptoms, blood data and comorbidity.

3.3. Imaging findings of the 1st MRI in SD patients

The site mostly involved sites with SD lesions were the lumbar area. Some had infection extending to the surrounding structures including the psoas muscle. The characteristics of SD and other infectious lesion of the 1st MRI are summarized in Table 3.

3.4. SFC volume and its correlates

In 20 SD patients with SFC, 17 patients had follow-up MRI. Nine, 5, 2 patients and 1 patient were performed the 2nd, 3rd, 4th and 5th MRI, respectively. Intervals from initial MRI were 24.4 ± 16.5, 38.9 ± 25, 71.3 ± 19.9 and 115 days, respectively. ICC of SFC volume measurements for the 1st to 5th MRI was 0.98, which was recognized as very good intra-observer reproducibility [18].

There was no relationship between presence of SFC on 1st MRI and initial mobility status (walk, on wheelchair or bedridden) of patients. Analysis between SFC volumes on 1st MRI and clinical data (BW, BMI, blood data and scores of the BI or FIM motor) found no statistically significant correlation. No significant correlation was observed between changes of SFC volume and the scores of the BI or FIM motor from the 1st to 2nd measurements. There was no significant difference in SFC prevalence of initial

MRI by comorbidity.

However, significant positive linear correlations were found between changes in SFC volume from the 1st to 2nd or last MRI and CRP (*x*, SFC volume change; *y*, CRP; $y = 1.1035x + 3.8547$, $R^2 = 0.60$, $p = .001$ and $y = 0.9099x + 5.4561$, $R^2 = 0.43$, $p = .01$, respectively; See Fig. 1). No significant correlation was found with changes of WBC or ESR. Plot of averages of SFC volume and blood inflammatory markers of WBC, CRP and ESR from the 1st to 3rd MRI in 8 patients shows a similar trend between volume of SFC and CRP (Fig. 2). Representative cases are presented in Figs. 3 and 4.

4. DISCUSSION

Subcutaneous adipose tissue consists of two layers of superficial and deep layers [9], and SFC is observed at the deep layer. These layers are structurally different. Fat lobules of the superficial layer are small and tightly packed within closely spaced septa, whereas those of the deep layer are large, sparse and much less organized [9]. Such anatomical difference in anatomy is considered to be one of the reasons for fluid collection.

In their investigation of non-SD patients, Shi *et al.* reported that degree of fluid collection on MRI was associated with increase in the BW in patients with disc disease or

radiculopathy [10]. In their low-weight subgroup, the prevalence of SFC was less than the obese group and was similar to that of the non-SD patients in our study. They speculated pathophysiology of SFC in obese patients was: (1) increased pressure of inferior vena cava due to increased intra-abdominal pressure followed by increased peripheral and capillary pressure, (2) increased circulatory volume and intravascular pressure due to obesity, and (3) increased peripheral capillary blood flow and permeability caused by reduced cutaneous vasoconstriction response to sympathetic activation in obese patients. In our study, however, there was no correlation between volumes of SFC on the 1st MRI and BW or BMI in SD patients. This result suggests presence of other factors related to SFC.

In SD patients, decreased body movement may contribute to formation of SFC. However, no significant correlation was found between physical conditions or BI/FIM motor indices and SFC. The same was the case for comorbidities of DM and others. These results may suggest presence of some specific mechanism for SFC in this study. SD may cause impairment of the vessels and lymphatics around the vertebra, leading to decreased lymphatic drainage. Such changes may increase permeability of not only vessel around vertebra, but also that of subcutaneous adipose tissue, because the lumbar subcutaneous vessels and lymphatics join into these around the vertebra [19]. Inflammation

of SD may spread to the structures around posterior portion of vertebra such as Facet joint, spinous process and erector spinae muscle. This may be one of the reasons for appearance of SFC.

Volume measurement of SFC was conducted using region growing method by Osirix. This method is relatively easy to select ROI semi-automatically and could be acceptable broadly, because ICC of SFC volume measurement that was conducted twice was very good.

No correlation was found between all biological data, including WBC, CRP and ESR, and SFC volume on the 1st MRI. It was probably because these values varied widely depending on each patient. However, when focused on changes between the 1st and 2nd MRI and the 1st and last MRI, significant relationships were observed correlated to corresponding changes in CRP, which normalizes quickly and is helpful in tracking recovery from SD [2, 7, 20]. As in Fig. 2, SFC volume changes are parallel to those of CRP, especially at the early stage, which relationship may make SFC volume changes an imaging marker for improvement of local inflammation.

No correlation was found between SFC volume changes and those of WBC or ESR. WBC isn't elevated in all patients with spinal infection and is often only slight elevated to normal in elderly and immunocompromised patients [2]. It also shows no

significant trend during treatment [21]. ESR is elevated in higher rate and is thought as useful marker [7, 21-23]. However, ESR may remain elevated to some degree for as long as 6 months in up to 75% of patients [24]. All patients don't show complete fall of ESR values after successful treatment. Therefore, persistent elevation of ESR doesn't necessarily indicate treatment failure [21]. Relatively slow reduction of ESR can also be observed in our results (see Fig. 2).

Limitations in this study include its retrospective nature and relatively small sample size. We could not acquire the constant follow-up MRI and biological data of all patients. We need further prospective study with larger populations. We couldn't obtain the all specimen from local lesions because of patient conditions. We should identify the microorganisims to diagnose SD definitely for all cases, but 15 SD patients were treated with antibiotics before the initial MRI. Although MRI should be performed before treatment, it may be difficult to do so on the acutely ill patients considering priority of treatment.

5. Conclusions

In conclusion, there has been no imaging marker for improvement of SD, despite increasing use of follow-up MRI examinations. In patients with SD, volume changes of SFC are highly correlated to changes of CRP and can be used to assess

treatment response by imaging.

Conflict of interest

All authors declare no conflict of interest.

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Figure legends

Fig. 1. Scatterplot of Δ CRP and Δ volume of SFC using difference values with regression lines. Each correlation between Δ CRP and Δ volume of SFC using difference values on 1st & 2nd MRI (A) and 1st & last MRI (B) is statistically significant (each $p < .05$).

Fig. 2. The relationships between volume of SFC and biological data in 8 patients (1st ~ 3rd MRI). We show the good relationships between volume of SFC and CRP. Values of WBC and ESR are indicated as each a thousandth and a tenth values.

Fig. 3. Seventy-one years old male with L4/5 discitis, epidural abscess at the level of L4/5 (not shown), and bilateral psoas abscess. Initial sagittal STIR image shows hyperintensity in the disc of L4/5 (A, arrowhead). Massive SFC is also seen (A, arrow). Hyperintensity in the disc of L5/S is physiological signal intensity. Axial T2WI shows bilateral psoas abscess (B, asterisk). On follow-up sagittal STIR (C) (11 days after treatment), hyperintensity in the disc of L4/5 disappears. Volume of SFC decreases (C, arrow). Improvement of right psoas abscess is also seen on follow-up axial T2WI after drainage (D). Left psoas abscess remains (D, asterisk). CRP values changed from 18.73 mg/dl at

the initial state to 1.9 mg/dl at 11 days after treatment.

Fig. 4 Sixty-six years old female with spondylodiscitis and prevertebral abscess (arrowhead) at and around Th5/6 on the initial STIR image (A). SFC is seen (A, arrow). Old compression fracture in Th10 is also shown. On follow-up sagittal STIR (B) (6 days after treatment), hyperintensity in Th5/6 and prevertebral space remains (arrowhead), but SFC disappears. In this case, CRP values decreased from 27.20 mg/dl to 5.6 mg/dl.

Table 1 Demographics of patients with spondylodiscitis.

Variables	N
Sex	Male 13 Female 11
Age (years)[a]	74.6 (59-89)
Body weight (kg)[b]	57.8 ± 18.6
BMI (kg/m^2)[b]	23.2 ± 7
Initial symptom presentation	
Back pain	9
Fever	5
Back pain + Fever	8
Others	2
Initial status	
Walk	6
Wheelchair	2
Bedridden	16
Comorbidity	
DM	10
CRF	5
Chronic liver disease	5
PSL user	4
Antibiotic Treatment before 1st MRI	
Yes	15
No	9

BMI: body mass index, CRF: chronic renal failure, DM: diabetes mellitus,

MRI: Magnetic resonance imaging, PSL: prednisolone. aRange, bMean ± SD.

Table 2 Culture results and identified microorganism.

Variable	N
Culture from local lesion	
Positive	7
Negative	5
Not performed	12
Blood culture	
Positive	14
Negative	9
Not performed	1
Positive culture from local lesion	
MSSA	1
Strptococcus bovis	1
Candida tropicalis	1
Escherichia coli	1
Klebsiella pneumoniae	1
Alpha-Streptococcus	1
Actinomyces spieces	1
Positive blood culture	
MSSA	5
MRSA	2
Alpha-Streptococcus	2
Escherichia coli	2
Streptococcus agalactiae	1
Strptococcus bovis	1
Strptococcus dysgalactiae	1
Sputum culture	
Mycobacterium tuberculosis	2

MRSA: methicillin-resistant Staphylococcus aureus, MSSA: methicillin-sensitive Staphylococcus aureus. There was positive overlap of cultures from local lesion and blood in 4 cases.

Table 3 The characteristics of spondylodiscits and other infectious lesion on the 1st MRI.

Variable	N
Site of involvement	
Thoracic	5
Lumbar	18
Thoracic + Lumbar	1
SD vs D (Mono:Multiple)	
Only D	4 (3:1)
Only SD	15 (13:2)
Only S	3 (1:2)
SD + D	2
Other infectious lesion	
Epidural	4
Prevertebral	4
Psoas	7
Multiple	4

D: discitis, S: spondylitis, SD: spondylodiscitis.

SD + D means spondylodiscitis with discitis of other level.

Multiple means more than 2 infectious lesions.

Supplementary Table 1 Mean WBC, CRP and ESR of all Patients.

	1st	2nd	3rd	4th	5th
WBC (μl)	11,071 ± 4,932 (24)	7,742 ± 3,294 (14)	6,975 ± 3,445 (8)	7,766 ± 2,558 (3)	8,900 (1)
CRP (mg/dl)	12.86 ± 12.08 (23)	4.30 ± 4.32 (15)	2.59 ± 3.97 (8)	0.80 ± 0.96 (3)	0.36 (1)
ESR (mm/h)	85.1 ± 32.6 (22)	77.3 ± 40.5 (14)	76.1 ± 40.8 (8)	38.3 ± 16.3 (4)	22 (1)

WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. Values are presented as mean ± SD, and in the parentheses are numbers of patients.

Figure 1A

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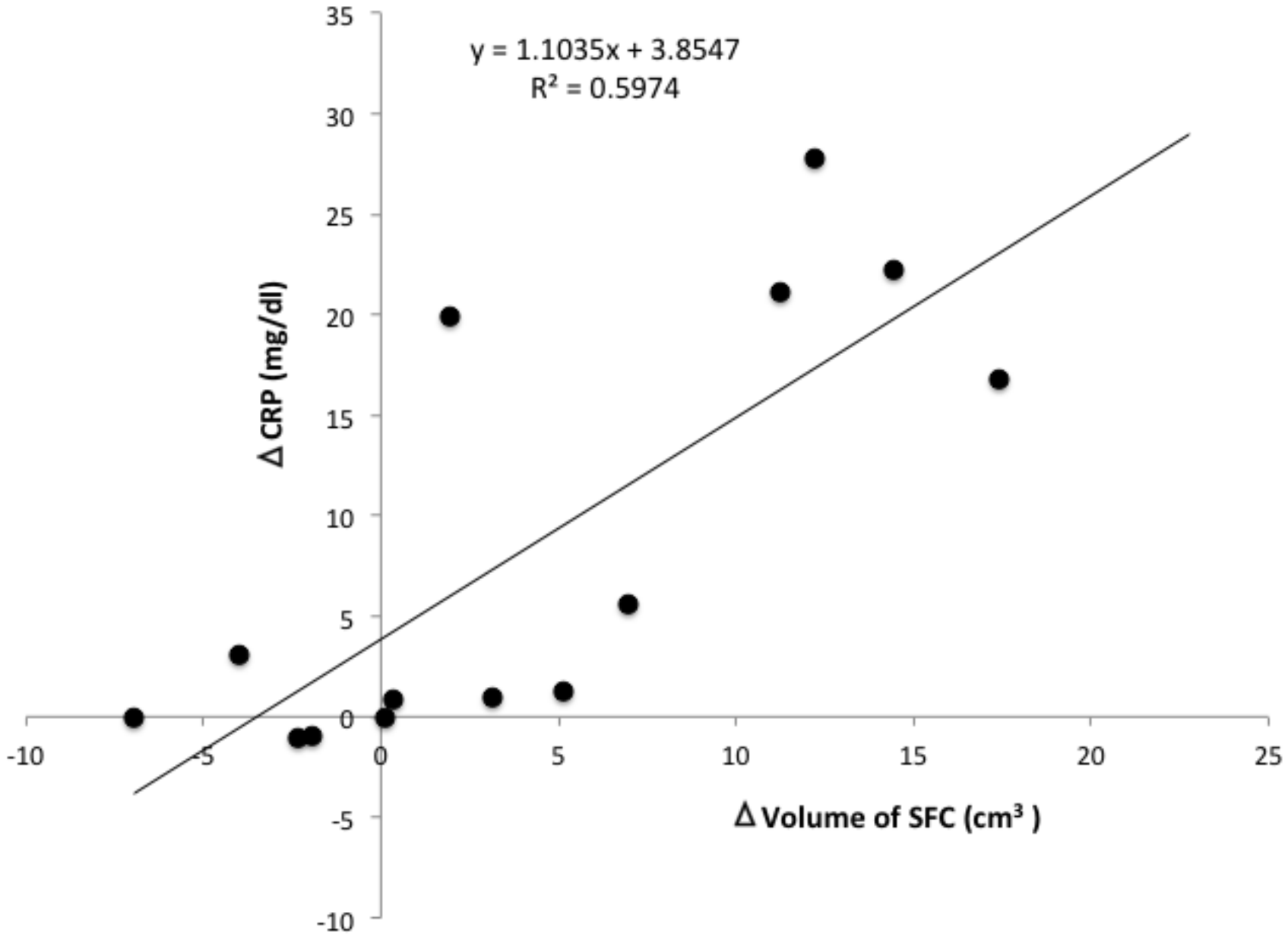

Figure 1B

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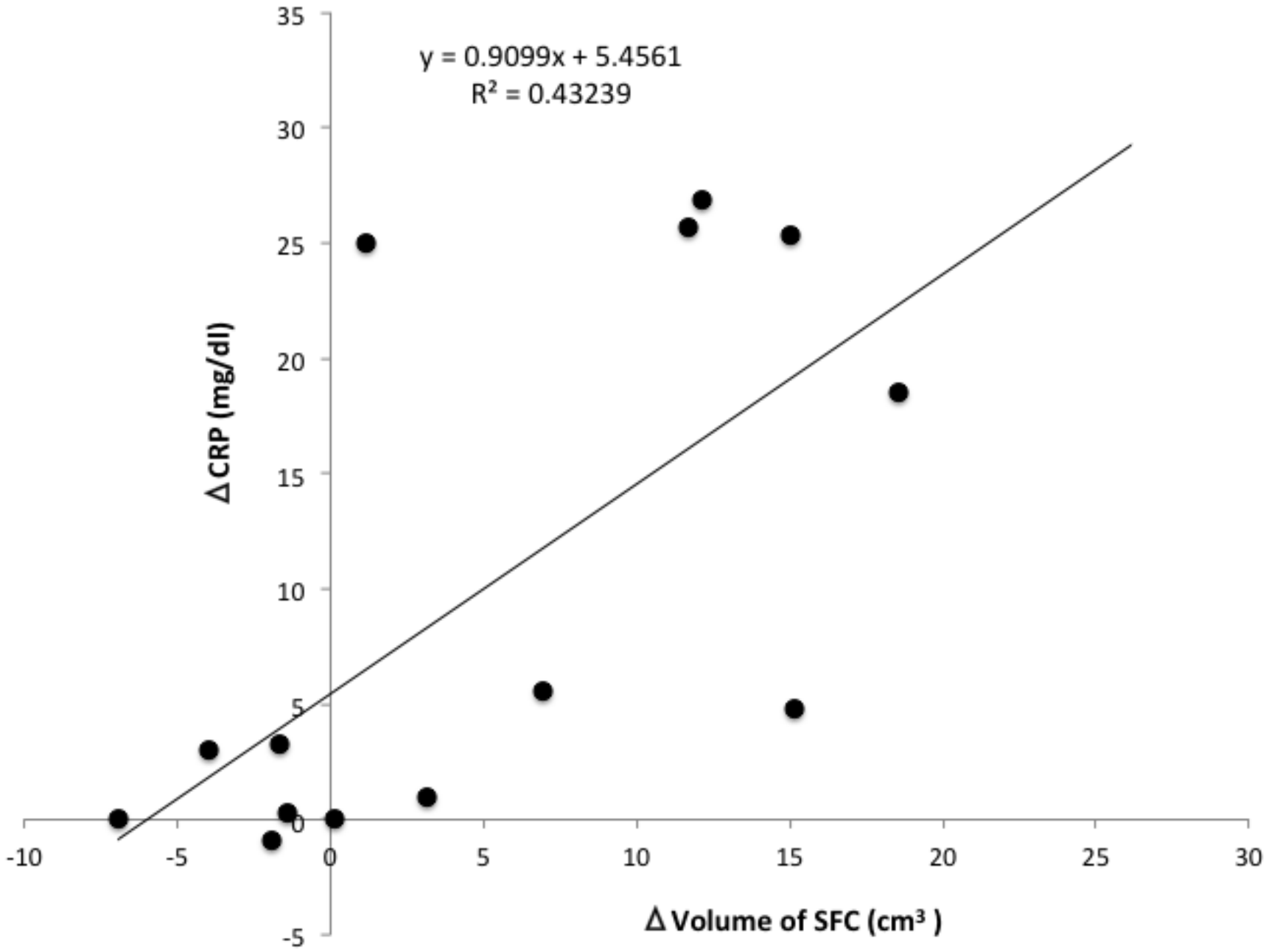

Figure 2

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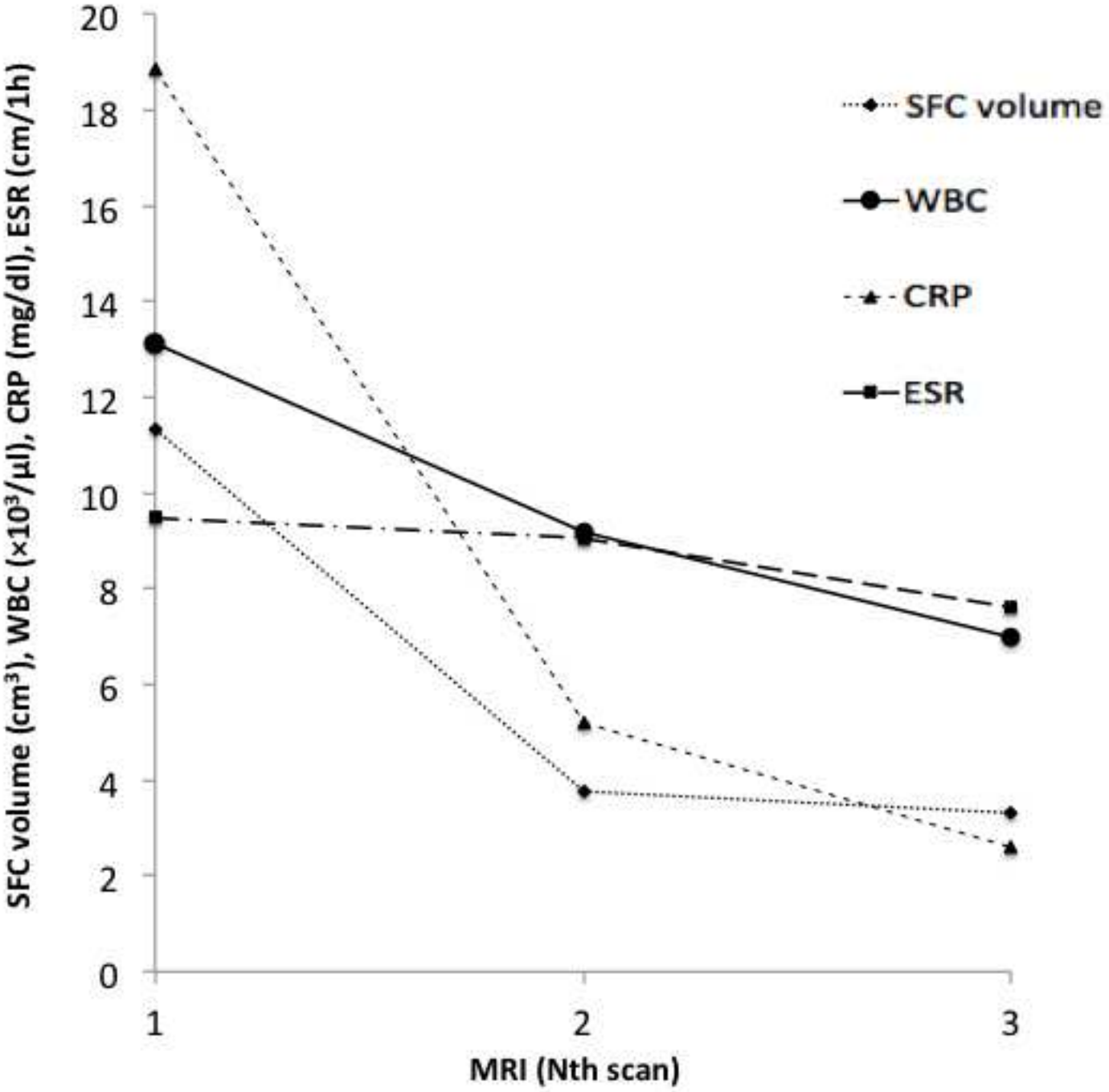

Figure 3

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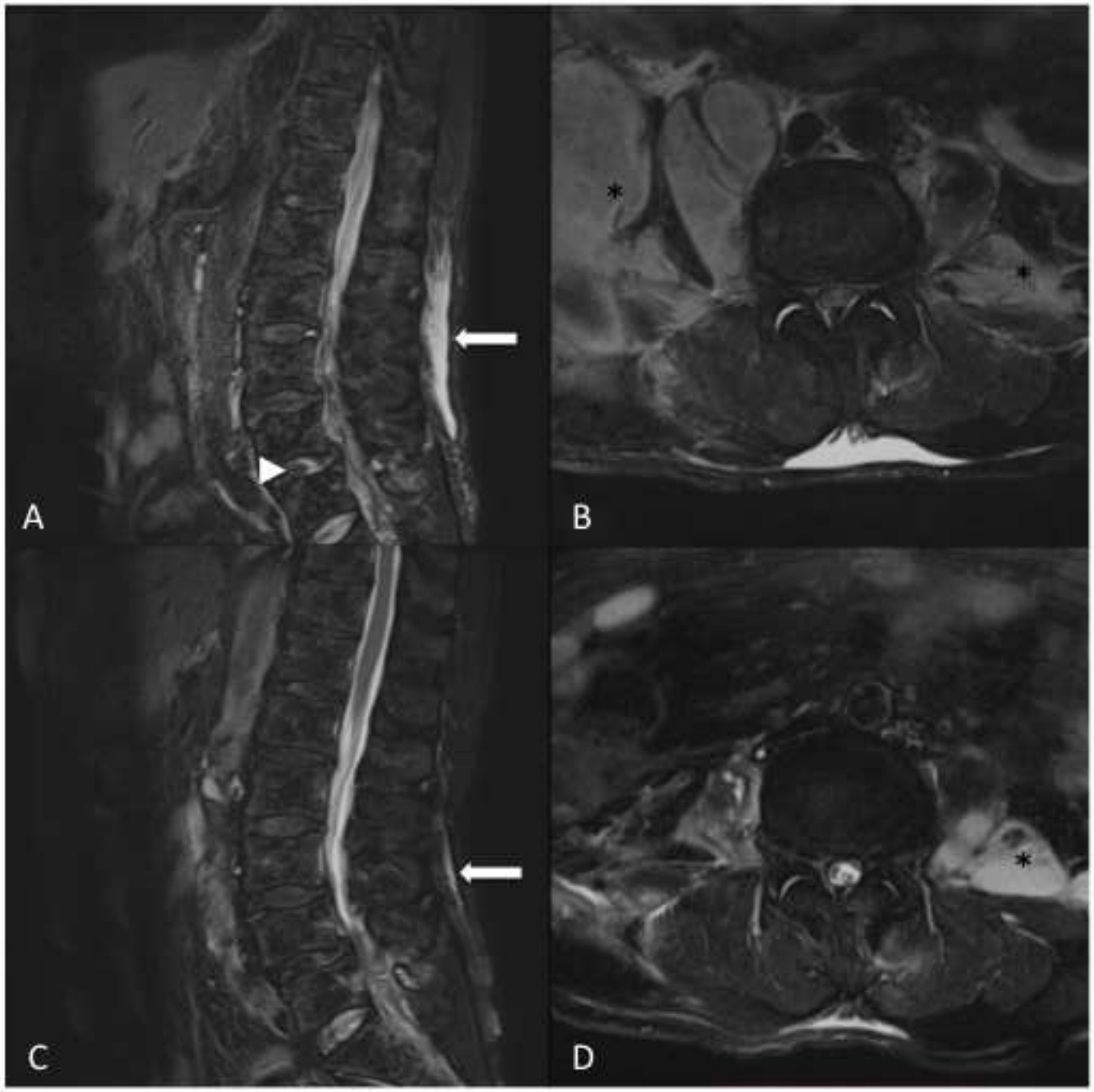

Figure 4

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