Biomarkers in Juvenile Systemic Sarcoidosis: A Case Report and Literature Review

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Case Report

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Abstract

Background: Juvenile sarcoidosis represents a spectrum of rare granulomatous inflammatory conditions characterized by non-caseating granulomas that can affect multiple systems. Nonetheless, no laboratory markers can conclusively indicate a diagnosis of sarcoidosis. In this report, we discuss the role of serum soluble interleukin-2 receptor (sIL-2r) levels in supporting the diagnosis of sarcoidosis in a child with ocular, renal, and pulmonary involvement. We further discuss trends in this marker, as well as serum angiotensin converting enzyme (ACE) and 1,25(OH)2D levels, in relation to disease activity and response to treatment.

Case Presentation: A previously healthy 14-year-old Arabic girl presented with fever, anorexia, and dyspnea upon exertion. She exhibited elevated levels of acute-phase reactants, anemia, elevated serum creatinine, and proteinuria. An eye exam revealed bilateral uveitis. High-resolution computed tomography (CT) of the chest revealed subpleural interlobar septal thickening with reticular changes and subtle ground glass opacities. The results of an extensive work-up to rule out infectious etiology, immune deficiency, malignancy, and other rheumatic diseases were unremarkable. Serum levels of sIL-2r were extraordinarily high at 18,589 U/L (normal range: 223–710 U/L), and the trend of subsequent measurements correlated with disease response and disease reactivation. Although ferritin levels were elevated at 1,136 ng/mL (normal: 13–68 ng/mL), bone marrow biopsy was negative for hemophagocytosis. Kidney biopsy revealed granulomatous interstitial nephritis with tubular atrophy. Serum ACE and 1,25(OH)2D levels were also elevated at diagnosis. The patient was treated with glucocorticosteroids, mycophenolate mofetil, and anti-tumor necrosis factor (anti-TNF). Clinical responses to such treatment were correlated with trends in serum sIL-2r and 1,25 (OH)2D levels, but not with trends in serum levels of ACE.

Conclusions: Our findings highlight the promise of sIL-2r as a marker of diagnosis and disease activity during the treatment period in patients with juvenile sarcoidosis. Further prospective studies involving large cohorts of patients with childhood sarcoidosis are required to elucidate the diagnostic and prognostic roles of serum sIL-2r levels.

Background

Juvenile sarcoidosis represents a spectrum of rare granulomatous inflammatory conditions, including monogenic forms associated with *NOD2* mutations [1]. Sarcoidosis is diagnosed based on clinical manifestations, radiographic findings, histopathologic detection of non-caseating granulomas in the affected organ, and exclusion of other diseases. However, no laboratory markers can conclusively indicate a diagnosis of sarcoidosis. Although serum angiotensin converting enzyme (ACE) is among the most commonly used diagnostic biomarkers for sarcoidosis, the test is non-specific and lacks sensitivity [1]. Hypercalciuria, hypercalcemia, and increased levels of 1,25-dihydroxy vitamin D (1,25(OH)2D) may also occur in patients with sarcoidosis due to over-production of 25-hydroxy vitamin D-1 α-hydroxylase [1, 2].

Recent studies involving adult patients have suggested that serum levels of soluble interleukin-2 receptor (sIL-2r) represent a superior, more sensitive biomarker than serum levels of ACE in supporting the diagnoses of both systemic and ocular sarcoidosis [3, 4]. Moreover, researchers have suggested that the level of sIL-2r correlates with the level of disease activity and may indicate multisystem involvement [5]. However, most studies of sarcoidosis biomarkers have been conducted among adult patients. In the present report, we discuss the role of sIL-2r levels when combined with serum ACE and 1,25(OH)2D levels in supporting the diagnosis of systemic sarcoidosis in a child with ocular, renal, and pulmonary involvement. Trends in levels of these markers are discussed in relation to disease activity and response to treatment. The Discussion section also includes a literature review of relevant biomarkers in juvenile sarcoidosis.

Case Presentation

A previously healthy 14-year-old Arabic girl presented with fever up to 39 °C, chills, night sweats, anorexia, decreased activity, and dyspnea upon exertion for two months duration. Systemic review revealed no signs of headache, changes in behavior, blurred vision, palpitations, chest pain, gastrointestinal manifestations, rashes, arthralgia, swollen joints, or peripheral swelling. She was hospitalized for 6 days in another institution for evaluation, at which time she exhibited increases in serum creatinine level (2.91 mg/dL; normal: 0.5–0.9. mg/dL), erythrocyte sedimentation rate (ESR) (38 mm/h; normal: 0–15 mm/h), C-reactive protein (CRP) level (67.8 mg/L; normal: 0–2.8 mg/L), and ferritin level (1,136 ng/mL; normal: 13–68 ng/mL). She also exhibited decreased hemoglobin level (8.4 g/dL; normal: 12–16 g/dL) but normal platelet count 246×10^3/mcl ($150–450 \times 10^3$/mcl), total white blood count (WBC) of 7×10^3/mcl ($4–11 \times 10^3$/mcl), and mildly elevated aspartate aminotransferase (AST) level (39 U/L; normal: 0–27 U/L). She was subsequently transferred to our hospital for further evaluation. Physical examination revealed stable vital signs. Although she was pale, the results of her cardiovascular, chest, and abdominal exams were normal. Neurologic findings were unremarkable, including those related to the cranial nerves, muscle strength, and gait. She did not exhibit rashes, palpable lymphadenopathy, or arthritis. Eye examination by an ophthalmologist revealed bilateral anterior uveitis, flares, keratic precipitates, vitritis, and perivascular sheathing.

A subsequent round of laboratory tests revealed decreased hemoglobin level (8.9 g/dL; normal: 12–15 g/dL), normal platelet count 246×10^3/mcl ($150–450 \times 10^3$/mcl), and WBC 7.08×10^3/mcl ($4–11 \times 10^3$/mcl) with low absolute lymphocyte count (ALC) of 1040 but normal absolute neutrophil count (ANC) and no eosinophilia. The ESR was 38 mm/h (normal: 0–15 mm/h), while CRP level was 67.8 mg/L (normal: 0–5 mg/L). Creatinine (3.21 mg/dL; normal: 0–0.9 mg/dL) and urea levels (54 mg/dL; normal: 18–45 mg/dL) were also elevated, as was the urine protein-to-creatinine ratio (0.39; normal: 0–0.2). Alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, and albumin levels were normal, while AST levels were mildly elevated at 39 U/L (normal: 0–27 U/L). Stool occult blood and calprotectin tests were negative. Blood and urine cultures for infectious diseases (QuantiFERON, *Bartonella henselae*, *parvovirus B19*, *Epstein–Barr* virus, and *Brucella melitensis* titers) were negative. Rheumatological work-

up for antinuclear antibodies, anti-DsDNA, anti-glomerular antibodies, antineutrophil cytoplasmic antibodies, and extractable nuclear antibodies (including anti-Jo-1 antibodies) yielded negative results. Immunological findings for C3 and C4 levels, CH50, and oxygen burst tests were normal. The immunoglobulin G (IgG) level 1165 mg/dl, IgG1 level 680 mg/dl, IgG2 level 373 mg/dl, IgG3 level 147 mg/dl, and IgG4 level 30 mg/dl were all within normal range. Flow cytometry for T cells, B cells, and natural killers (NK cells) revealed low absolute CD4 and CD8 numbers, although percentages remained normal. WBC at time of flow cytometry was 10,510 (ANC 8720 and ALC 830), CD4 absolute count was 310.7 uL (normal 400–2100), CD4% was 40.3% (25–48%), CD8 absolute count was 101.2 uL (200–1200), CD8% was 13.1% (9–35%), CD4:CD8 ratio was high at 3.01, CD19 absolute count was 106.5 uL (200–660), CD19% was 13.8% (8–24%), CD3 absolute was 432.3 uL (800–3500), CD3% was 56.1% (58–78%), and NK absolute count was 227 uL (70-1200) and NK% was, 29.5% (6–27%). Work-up for macrophage activation syndrome revealed increased ferritin levels at 1,136 ng/mL (normal: 13–68 ng/mL), prolonged partial thromboplastin time (PTT) (45.4 seconds; normal: 28–37.9 seconds), normal prothrombin time (PT) and international normalized ratio (INR), increased fibrinogen levels (445 mg/dL; normal: 212–433 mg/dL), and increased d-dimer levels at 2.28 mcg/ml (normal: 0–0.5 mcl/mL). Serum levels of sIL-2r were very high at 18,589 U/L (normal: 223–710 U/L). Bone marrow biopsy revealed cellular marrow with granulocytic hyperplasia and was negative for hemophagocytosis. Tests for markers of sarcoidosis revealed elevated levels of sIL-2r, 1,25(OH)2D, and serum ACE as shown in Table 1.

Table 1
Markers of disease activity at the time of diagnosis and throughout the treatment period

Test (weeks)	0	2	4	8	10	14	18	22
Hgb g/dL (12–15 gm/dl)	8.9	9	11.7	15.1	10.9	12.7	14.1	15
WBC (4–11 × 10(3)/mcL)	7.08	10.23	9.43	12.62	6.34	12.05	8.29	5.68
Platelets (150–450 × 10(3)/mcL)	246	375	216	238	318	234	253	275
CRP mg/L (< 5 mg/L)	67.8	3.96	< 0.3	6.91	64.7	8.57	1.79	0.92
ESR mm/h (< 15 mm/h)	38	30	2	1	23	34	10	2
ALT (0–23 U/L)	21	15	14	20	17	13	11	10
AST (0–27 U/L)	39	13	10	16	13	13	12	14
LDH (0-300 U/L)	289	-	207	521	320	239	261	254
Albumin g/dL (3.2–4.5 g/dL)	3.3	3.8	4.3	4.5	3.9	4.3	4.7	5
Creatinine mg/dL < 0.9 mg/dL)	4.36	2.02	0.94	0.92	1.47	0.85	0.88	0.82
Pro:Cr (0–0.2)	0.56	-	0.21	0.13	0.3	0.21	0.11	0.09

Week 0 refers to baseline labs prior to treatment. Treatment course as described in the text ensued after renal biopsy and baseline test results. Results of laboratory tests were clustered and reported within the nearest week.

Abbreviations: ACE, serum angiotensin converting enzyme; Ca:Cr, calcium-to-creatinine ratio; CRP, C-reactive protein; D3, 1,25 Dihydroxyl vitamin D; ESR, erythrocyte sedimentation rate; Hgb, hemoglobin concentration; Pro:Cr, protein-to-creatinine ratio; sIL-2r, soluble interleukin 2 receptor.

Test (weeks)	0	2	4	8	10	14	18	22
Ca:Cr (< 260) mg/g ceat	57	267	-	162	165	-	153	-
D3 pg/mL (19.9–79.3 pg/mL)	168	23.6	57.7	108	> 200	68.8	87.3	54.6
sIL-2r U/mL (223–710 U/ml)	18,589	7,582	909	1,837	7,394	2086	826	726
ACE U/L (14–82 U/L)	160	108	17	15	64	28	16	18
Week 0 refers to baseline labs prior to treatment. Treatment course as described in the text ensued after renal biopsy and baseline test results. Results of laboratory tests were clustered and reported within the nearest week.								
Abbreviations: ACE, serum angiotensin converting enzyme; Ca:Cr, calcium-to-creatinine ratio; CRP, C-reactive protein; D3, 1,25 Dihydroxyl vitamin D; ESR, erythrocyte sedimentation rate; Hgb, hemoglobin concentration; Pro:Cr, protein-to-creatinine ratio; sIL-2r, soluble interleukin 2 receptor.								

Abdominal ultrasonography revealed mild hepatosplenomegaly and enlarged kidneys with increased parenchymal echogenicity. Non-contrast CT scans of the chest and abdomen revealed multiple posterior cervical, submandibular, left supraclavicular, mesenteric, and retroperitoneal lymph nodes with bilateral lung infiltrates. High-resolution CT of the chest revealed subpleural interlobar septal thickening with reticular changes and subtle ground glass opacities. Flexible bronchoscopy revealed normal airway mucosa and bronchoalveolar lavage, excluding infections such as histoplasmosis, tuberculosis, and fungal infection. Echocardiography and electrocardiography findings were normal. Spirometry and lung volumes did not indicate obstructive or restrictive ventilatory defects, respectively; however, diffusing capacity (corrected for alveolar volume) was moderately reduced (62% of the expected value). Renal biopsy revealed diffuse interstitial nephritis with multifocal non-caseating granulomata and mild-to-moderate tubulointerstitial fibrosis. Immunofluorescence staining results were negative. Electron microscopy revealed no immune-type electron-dense deposits. Glomerular basement membranes were normal in texture and contour. The tubulointerstitium exhibited inflammation and a mild increase in fibrosis. Acid-fast and Grocott-Gomori's methenamine silver stains for organisms including acid-fast bacilli and fungal organisms were negative.

We diagnosed the patient with juvenile sarcoidosis, following which we initiated treatment with methylprednisolone succinate (30 mg/kg/day pulse therapy for 3 consecutive days, followed by 2 mg/kg/day intravenously). Oral treatment with prednisone 60 mg (2 mg/kg) was continued upon discharge based on a tapering schedule. Prednisolone eye drops were prescribed for topical use and tapered successfully. Mycophenolate mofetil (MMF) (750 mg; body surface area: 1.36 m^2) was administered twice daily at onset, along with infliximab infusions (dose 0 was 3 mg/kg followed by

5 mg/kg 2 weeks later, then every 4 weeks). Disease markers were measured frequently throughout the disease course as shown in Table 1 and Fig. 1. During prednisone tapering, the patient became febrile and fatigued when the dose of prednisone was at 20 mg daily, and she exhibited elevated levels of disease markers during that time. The symptoms may also have been triggered by a viral infection 1 week earlier and MMF treatment was thus halted for 1 week. The prednisone dose was increased back to 60 mg once daily, which resulted in improved levels of disease markers as shown in Fig. 1. These improvements also coincided with the switch to subcutaneous adalimumab (40 mg) every other week after completing five infusions of infliximab due to infliximab infusion-related side effects. The patient continues to exhibit excellent clinical and laboratory responses. The patient did not receive any ACE inhibitors.

Discussion

Juvenile sarcoidosis is rare and difficult to diagnose. Although current laboratory tests can guide diagnosis, they are non-specific, and the results should be interpreted in the context of clinical manifestations, imaging findings, and characteristic histological features. Initial work up typically includes basic laboratory tests that often reveal non-specific changes such as elevated ESR and CRP, mildly decreased hemoglobin values, moderate leukopenia, leukocytosis, and/or eosinophilia [6]. As in the present case, abnormalities in liver and kidney function may also be observed, in which case findings from liver or kidney biopsies can aid in histological diagnosis. Rates of hypercalcemia have varied among studies (2–63%), although patients are rarely symptomatic [1, 2]. Typically, patients exhibit increased production of 1,25(OH)2D with low levels of 25-hydroxy-vitamin D and no increases in parathyroid hormone levels [2, 7, 8, 9]. In our patient, 1,25(OH)2D levels were elevated at the time of diagnosis and were more correlated with disease reactivation than serum ACE levels.

Historically, the Kveim–Siltzbach skin test has been used to guide diagnosis, with high sensitivity and moderate specificity [7, 10]. The test is performed by injecting a homogenate of human sarcoidosis lesions intracutaneously, followed by a biopsy 6 weeks later. Unfortunately, this test has a long delay and is no longer widely available for clinical use. Serum lysozyme (LZM) and ACE levels were first highlighted as markers of sarcoidosis in 1973 and 1975, respectively [11]. LZM is secreted from monocytes and polymorphonuclear leukocytes, although the epithelioid cells of the granuloma are the source of serum ACE and LZM when they are both elevated. Moderate increases in serum LZM activity occur in patients with conditions such as acute bacterial infections, leukemoid reactions, megaloblastic anemia, and increased granulocytic turnover. Because serum LZM is less specific for sarcoidosis than serum ACE, the diagnostic value of the test may be limited [11]. However, serum LZM seems suitable for disease monitoring in proven cases. In addition, serum LZM levels demonstrate a significant tendency to increase as the number of organs involved increases. Therefore, the LZM level is regarded as a prognostic indicator rather than a diagnostic tool [11, 12, 13].

The serum ACE level is commonly used as a diagnostic biomarker for the diagnosis of sarcoidosis. ACE is a dipeptidyl-carboxy-peptidase first described as an indicator of diagnosis and response to treatment

by Jack Lieberman in 1976. Early studies by Lieberman demonstrated that serum ACE levels are elevated in 90% of patients with sarcoidosis. In some cases, increased serum ACE levels can also predict subsequent changes in clinical status [11]. Later studies reported that serum ACE levels are elevated in approximately 30–80% of adult patients with sarcoidosis, with a sensitivity and specificity of approximately 72% and 60%, respectively [14]. Furthermore, many studies of adult patients with sarcoidosis have reported no significant differences in serum ACE levels between patients with active and inactive disease [11, 14, 15]. Although only a few studies have been conducted in children, their results suggest that serum ACE levels are correlated with disease activity in some cases [9, 16, 17, 18]. However, caution is required when interpreting the significance of serum ACE levels, as the reference interval for the test is age-dependent, and healthy young children may exhibit normal values that are 40–50% higher than those for adults [11, 16, 17]. It is also important to note that serum ACE levels may also be increased in patients with pathologies other than sarcoidosis, such as hyperthyroidism, cirrhosis of the liver, diabetes mellitus, Gaucher's disease, silicosis, and malignancies. Furthermore, other factors may affect the production of ACE, such as genetic factors and the use of ACE inhibitors [11, 17, 19, 20]. Therefore, serum ACE levels are considered supportive rather than definitive of a sarcoidosis diagnosis. In our patient, the serum ACE level was twice the normal value at the time of diagnosis, supporting the diagnosis of sarcoidosis given the patient's overall presentation and other features of the disease. As expected, serum ACE levels decreased rapidly after initiating treatment; however, at the time of disease reactivation, levels remained within the normal range despite an increase as shown in Fig. 1.

Various studies have assessed the applicability of other markers in adult patients with sarcoidosis, including adenosine deaminase (ADA) activity, serum amyloid A (SAA) levels, and sIL-2r levels [11, 14, 15, 21]. None of these markers has been extensively studied in patients with juvenile sarcoidosis. Only serum ACE and 1,25(OH)2D levels have been routinely measured in children with sarcoidosis, and the diagnostic and prognostic roles of other biomarkers in such patients remain to be fully determined [9, 16, 17, 18]. ADA is an enzyme involved in purine catabolism that is produced by mononuclear cells and lymphocytes. ADA is widely distributed in human tissues, and the soluble form gives rise to elevated serum levels. Previous studies have reported that serum ADA activity is increased in adult patients with sarcoidosis, especially in untreated patients. However, some studies have reported no significant differences in levels of ADA activity between patients with active and inactive disease [14, 22]. SAA is a marker of inflammation, and its relationship with sarcoidosis activity has been explored in some studies. In one study, SAA levels were elevated in patients with active disease, when compared to those in controls and patients with inactive disease, suggesting that SAA can be used as a marker of disease activity [14]. The role of SAA monitoring in childhood sarcoidosis remains unknown, especially since SAA can be elevated in other inflammatory conditions such as autoinflammatory syndromes.

Serum sIL2-r level has been regarded as a promising biological marker of sarcoidosis in adult patients [3]. The α chain of the IL-2 receptor (also known as CD25) is overexpressed by activated and regulatory T-cells and can be secreted from the cell membrane in a soluble form (sIL-2r) during disease activation. Therefore, sIL-2r is considered a surrogate marker for T-cell activation in patients with conditions such as rheumatoid arthritis, systemic lupus erythematosus, IgG4-related disease, and sarcoidosis. However, it

remains unclear whether sIL-2r is produced to combat sarcoidosis-associated immune activation or whether it plays an active role in the pathogenesis of the disease [3]. In one study, elevated serum sIL-2r exhibited superior diagnostic sensitivity and specificity when compared to serum ACE in a group of adult patients with suspected sarcoidosis (sIL-2r: sensitivity, 88%; specificity, 85%; ACE: sensitivity, 62%; specificity: 76%) [3]. Serum sIL-2r levels have also been used to diagnose ocular, pulmonary, and neurosarcoidosis in adult patients [4, 23, 24]. In one study comparing sIL-2r and serum ACE as screening markers for sarcoidosis in adult patients with uveitis, elevated sIL-2r was a more effective marker for sarcoidosis than ACE in patients with uveitis, with a specificity of 94% and sensitivity of 98%. In contrast, ACE was associated with a specificity of 99.5% but a sensitivity of only 22% [4]. In our patient, we evaluated sIL-2r levels as part of the workup for suspected macrophage activation syndrome, as she was febrile and exhibited elevated ferritin levels. The extraordinarily high sIL-2r level of 18,589 U/L (normal range: 223–710 U/L) was intriguing but the bone marrow study was negative for hemophagocytosis. Moreover, we had received the results for elevated serum ACE and 1,25(OH)2D levels, and the patient had undergone renal biopsy that revealed diffuse interstitial nephritis with multifocal non-caseating granulomata. Therefore, we interpreted the elevated sIL-2r level as a marker for sarcoidosis presenting with ocular, renal and pulmonary involvement and decided to follow the trend of this test closely. This interpretation was supported by the increased trend of two markers during disease reactivation (sIL-2r and 1,25(OH)2D), the bone marrow study result (negative for hemophagocytosis), and the promising reports of sIL-2 as a disease marker in adult onset sarcoidosis [3, 4, 23, 24].

We monitored sIL-2r levels along with the two other commonly used markers: serum ACE and 1,25(OH)2D levels. Given the short turnaround time for such tests, these three markers were rather useful for determining responses to treatment and for timely decision-making in our patient. Further prospective studies including larger cohorts of children with sarcoidosis are required to fully elucidate the diagnostic and prognostic roles of the markers noted in this review including serum sIL-2r levels. Until then, we propose that a group of markers should be utilized in order to identify the tests that most closely correlate with disease activity in each patient. This may prove difficult due to limitations in test availability, the cumulative cost of testing, and the turnaround time required to obtain results in some centers.

Conclusion

Our findings highlight the promise of sIL-2r as a marker of diagnosis and disease activity during the treatment period in patients with juvenile sarcoidosis when used in conjunction with other markers such as serum ACE and 1,25(OH)2D. Further prospective studies involving large cohorts of patients with childhood sarcoidosis are required to elucidate the diagnostic and prognostic roles of sIL-2r, and to identify other markers of disease in patients with juvenile-onset sarcoidosis.

Abbreviations

ACE
angiotensin converting enzyme

1,25(OH)2D
1,25 Dihydroxyl vitamin D
sIL-2r
soluble interleukin 2 receptor

Declarations

Ethics approval and consent to participate

Not required

Consent for publication

Written consent was obtained.

Availability of data and materials

Data sharing was not applicable to this article, as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SA is a second-year pediatric resident who provided patient care, reviewed medical records, conducted a literature review, and drafted the manuscript. HSM and PR provided patient care, edited the manuscript, and conducted a literature review. FBM is the primary rheumatologist and mentor for SA. FBM provided patient care and contributed to drafting the manuscript and literature search. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Figures

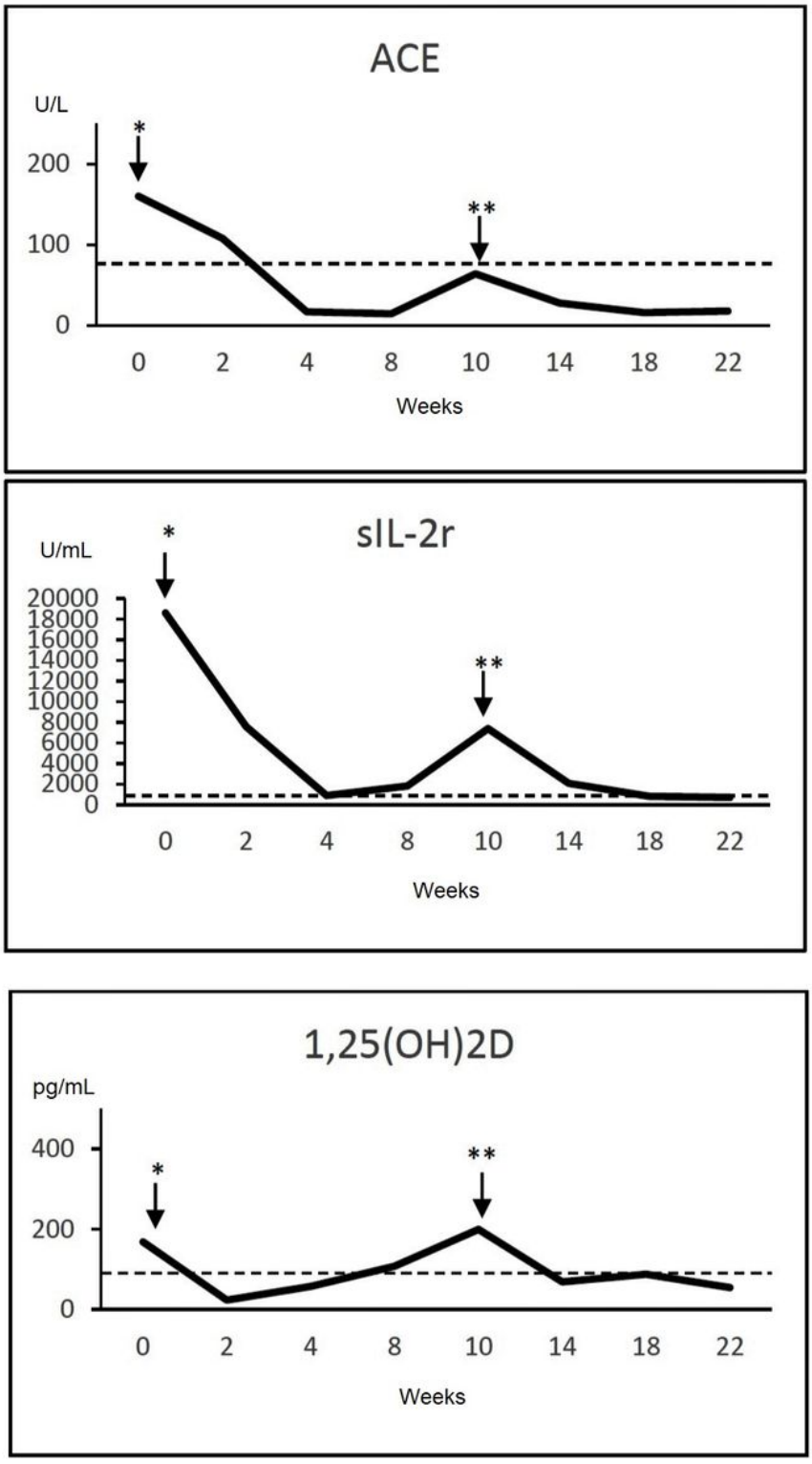

Figure 1

Trends in serum ACE, sIL-2r, and 1,25(OH)2D levels at the time of diagnosis and throughout the treatment period. * The first arrow indicates levels at the time of diagnosis, followed by treatment with systemic glucocorticosteroids, mycophenolate mofetil, and infliximab. ** The second arrow indicates the time of disease flare-up and increased doses of prednisone (60 mg daily). Shortly thereafter, the patient was

switched from infliximab to adalimumab due to an infusion-related reaction (see text). ACE: angiotensin converting enzyme; sIL-2r: soluble interleukin-2 receptor; 1,25(OH)2D: 1,25-dihydroxy vitamin D.