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Case Report

# A case of subacute combined degeneration of the spinal cord due to folic acid and copper deficiency

Takuji Nakamura [a,c,*], Masanori Nishi [a], Mihoko Rikitake [b], Daisuke Koga [a], Junya Eto [a,d], Daisuke Tajima [a,e], Shuji Toda [b], Muneaki Matsuo [a]

[a] Department of Pediatrics, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
[b] Department of Pathology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
[c] Department of Pediatrics, National Hospital Organization Ureshino Medical Center, 2436 Ureshino, Saga 843-0393, Japan
[d] Department of Pediatrics, Saga-ken Medical Center Koseikan, 400 Nakabaru, Kase-machi, Saga 840-8571, Japan
[e] Department of Pediatrics, Karatsu Red Cross Hospital, 2430 Watada, Karatsu, Saga 847-8588, Japan

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**Abstract**

Subacute combined degeneration of the spinal cord (SACD) is a rare neurologic disorder manifesting progressive symptoms of paresthesia and spastic paralysis. Herein we present an autopsy case of SACD caused by folic acid and copper deficiency. A 16-year-old male presented with gradually worsening unsteady gait, and bladder and rectal dysfunction. He had a medical history of T-cell acute lymphoblastic leukemia (T-ALL), diagnosed 1.5 years previously. The patient had undergone chemotherapy, including methotrexate, as well as allogeneic bone mallow transplantation. Laboratory tests revealed normal vitamin $B_{12}$ and methylmalonic acid concentration, but reduced serum copper, ceruloplasmin and folic acid concentrations. Magnetic resonance imaging revealed symmetrical T2 signal hyperintensities in the posterior and lateral spinal cord. The patient was treated with oral copper, oral folate, and intravenous vitamin $B_{12}$. A month after this treatment, the patient's symptoms were unchanged, and 2 months later he died of acute adrenal insufficiency. The pathological findings of the spinal cord were compatible with SACD. Because SACD is usually reversible with early treatment, it should be suspected in high-risk patients undergoing chemotherapy or those who are malnourished with characteristic symptoms of SACD, even in young patients.


*Keywords:* Subacute combined degeneration of the spinal cord; Folic acid deficiency; Copper deficiency; Myelopathy

## 1. Introduction

Subacute combined degeneration of the spinal cord (SACD) is a rare neurologic disorder manifesting progressive symptoms of paresthesia and spastic paralysis. Although SACD is usually caused by vitamin $B_{12}$ deficiency, other risk factors, including deficiencies in folic acid or copper, are known to be contribute to SACD [1–3]. SACD is rarely seen in childhood or adolescence.

*Abbreviations:* SACD, subacute combined degeneration of the spinal cord; T-ALL, T-cell acute lymphoblastic leukemia; MTX, methotrexate; NEL, nelarabine; CDM, copper deficiency myelopathy

* Corresponding author at: Department of Pediatrics, National Hospital Organization Ureshino Medical center, 2436 Ureshino, Saga 843-0393, Japan.
*E-mail address:* nakamurat@uresino.go.jp (T. Nakamura).

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Herein we present a case of 16-year-old male with SACD caused by folic acid and copper deficiency.

## 2. Case report

A 16-year-old male presented with gradually worsening unsteady gait, and bladder and rectal dysfunction. He had been diagnosed as having T-cell acute lymphoblastic leukemia (T-ALL) 1.5 years previously. The patient had undergone a course of chemotherapy (JACLS ALL-02 HR protocol; prednisolone, dexamethasone, vincristine, THP-adriamycin, cyclophosphamide, cytosine arabinoside, methotrexate (MTX), 6-mercaptopurine, L-asparaginase) for his T-ALL. However, after 10 months in remission, the patient's leukemia relapsed without central nervous system (CNS) involvement and he was treated with two courses of nelarabine (NEL, 650 mg/m$^2$/day, for 5 days). Because the NEL was not effective against the leukemia, the patient underwent additional chemotherapy (JACLS ALL-F02 reinduction therapy; prednisolone, dexamethasone, vincristine, THP-adriamycin, cyclophosphamide, cytosine arabinoside, MTX, 6-mercaptopurine, L-asparaginase, etoposide, mitoxantrone, vindesine). Four days after starting the reinduction therapy, the patient was diagnosed with perforated appendicitis and underwent an appendectomy. He could not walk due to surgical pain and disuse syndrome after the operation. Three months after the appendectomy, the patient underwent an allogeneic bone mallow transplantation. After the transplantation and treatment for graft-versus-host disease (tacrolimus, MTX, prednisolone), the patient developed bladder and rectal dysfunction. Placement of a urethral catheter was necessary because of difficulties urinating.

On examination, muscle tone in the patient's upper and lower limbs was decreased. Muscle weakness and atrophy was noted in all four limbs, particularly the lower limbs. The patient was not able to stand with support. Upper limb reflexes were diminished, whereas lower limb reflexes were brisk with bilateral extensor plantar responses. The vibration sense in the upper limbs was slightly decreased, and proprioception in the upper limbs was normal. The vibration sense in the lower limbs was absent, and proprioception in the lower limbs was decreased. The urinary incontinence and micturition urgency were not observed as urethral catheter was placed. The constipation was absence, but anal leakage was presence.

Blood investigations revealed a red blood cell count of $2.51 \times 10^6$/μL, hemoglobin 7.9 g/dL, hematocrit 23.4%, mean corpuscular volume 93.2fL, mean corpuscular hemoglobin 31.5 pg, mean corpuscular hemoglobin concentration 33.8%, total leukocyte count 3,600/μL, platelet count 38,000/μL and serum vitamin $B_{12}$ > 1500 pg/mL. Concentrations of methylmalonic acid and serum zinc (88 μg/dL; normal 65–110 μg/dL) were normal, whereas serum total homocysteine was increased (28.9 nmol/L; normal 3.7–13.5 nmol/L). Decreases were noted in serum folate (2.7 ng/mL; normal > 3.1 ng/mL), copper (54 μg/dL; normal 75–10 2.8 μg/dL), and ceruloplasmin (12.5 mg/dL; normal 21–37 mg/dL) concentrations.

Spinal magnetic resonance imaging (MRI) sagittal $T_2$-weighted images (T2WI) showed diffuse hyperintensity in the posterior spinal cord at Th7–12 (Fig. 1A), whereas spinal MRI axial T2WI showed symmetrical hyperintensity in the posterior and lateral spinal cord (Fig. 1B).

The patient was treated with oral copper (0.6 mg/day), oral folate (15 mg/day), and intravenous vitamin $B_{12}$ (1000 μg/day). However, after 1 month on this treatment, there was no change in his symptoms. Two months later, the patient died of acute adrenal insufficiency. Because his family agreed to a general autopsy, spinal histopathology was obtained.

## 3. Autopsy findings

The myelin sheath had disappeared in the posterior and lateral columns of Th7–12 (Fig. 2A, B). The disappearance of this myelin sheath was in accordance with the high-intensity areas on the spinal MRI (T2WI). Myelin in the posterior and lateral columns of Th7–12 was not stained with Luxol fast blue, which is commonly used to detect demyelination in the CNS (Fig. 2A). Immunohistochemical staining with anti-glial fibrillary acidic protein antibody and anti-CD68 antibody demonstrated increased microglia/macrophage infiltration in the demyelinated lesion. Neither astroglia nor lymphoblasts were observed (Fig. 2C–E). Axonal spheroids, which indicate axonal damage, were observed in the lesion (Fig. 2C). These pathological findings were compatible with SACD.

A brain autopsy was not performed. Extreme atrophy was seen in the bilateral adrenal cortex. Adhesions after the appendectomy were seen in the ileocecum, but there was no intestinal obstruction. The bone marrow was hypoplastic and fatty. A few myeloperoxidase-positive blast cells were seen in the bone marrow. The lymphoblastic infiltration, thrombus formation, or ischemia were not observed in the general organs.

## 4. Discussion

SACD is a rare cause of progressive demyelination of the dorsal and lateral columns of the spinal cord. Early manifestations associated with SACD are paresthesia of the lower limbs, loss of touch, vibration, and pain senses, and loss of proprioception. Further advanced manifestations are spastic paralysis, ataxia and anesthesia of the lower limbs and trunk. The pathogenesis of

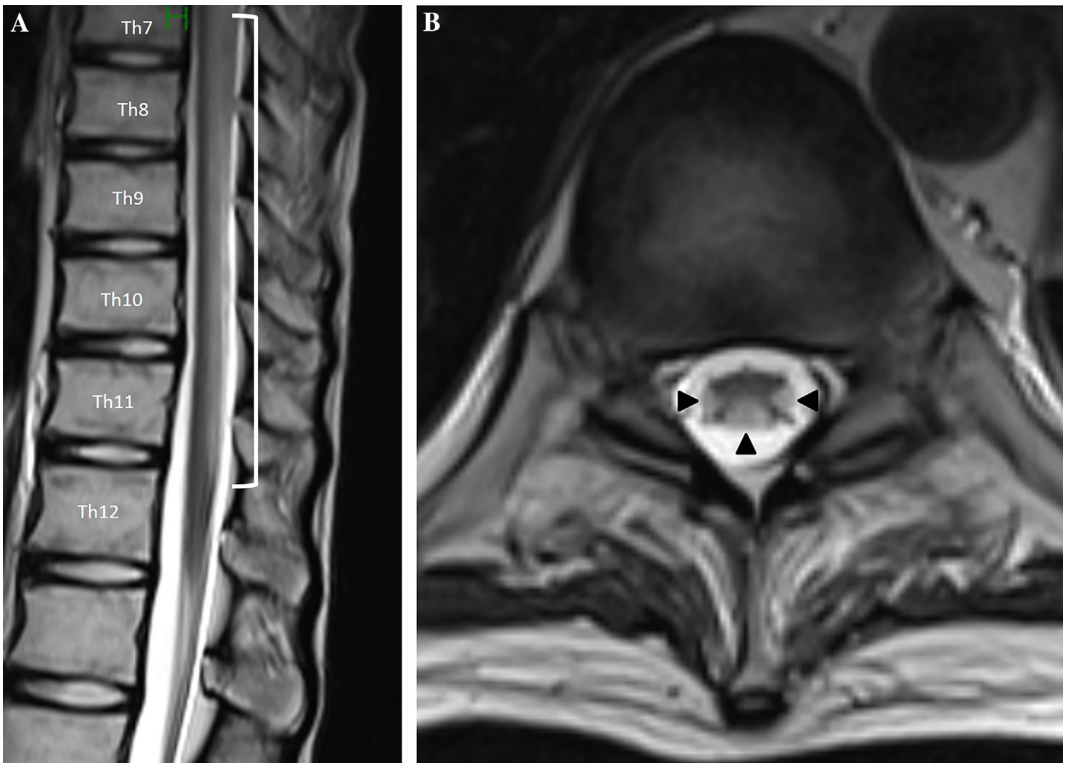


Fig. 1. (A) Spinal magnetic resonance imaging (MRI) sagittal $T_2$-weighted image (T2WI) showing diffuse hyperintensity in the posterior spinal cord at Th7–12 and (B) spinal MRI axial T2WI image showing symmetrical hyperintensity in the posterior and lateral spinal cord (*arrows heads*).

SACD remains unclear. Although SACD is usually caused by vitamin $B_{12}$ deficiency, it may also be caused by copper and folic acid deficiencies [1–3]. Our patient was not vitamin $B_{12}$ deficient, but he was found to be folic acid and copper deficient after a course of chemotherapy that included MTX for T-ALL.

In the present case, the patient's folic acid deficiency perhaps resulted from prolonged fasting because of the appendectomy and the administration of MTX. Although folic acid deficiency is common, folic acid deficiency-induced myelopathy is rare [1]. Folic acid deficiency-induced myelopathy is treated with folic acid supplementation [1]. Although SACD caused by folic acid deficiency is known to have a good prognosis, our patient did not respond to oral folate treatment.

Copper deficiency can be caused by ingestion of excess zinc, impaired intestinal absorption, nephrotic syndrome, and parenteral nutrition. In addition, this condition is seen, albeit rarely, in malnourished infants [2]. In the present case, the patient's copper deficiency could have resulted from his prolonged fasting and parenteral nutrition. In 2001, Schleper and Stuerenburg [5] reported the first case of copper deficiency-associated myelopathy in a 46-year-woman, after which 55 cases of copper deficiency myelopathy (CDM), which closely mimics SACD, were reported by Jaiser and Winston [4]. In the latter study, the age at presentation ranged from 30 to 82 years. The present patient is the youngest in the case reports of SACD caused by copper deficiency. CDM is treated with copper supplementation. In general, SACD caused by copper deficiency is known to have a poor prognosis, but early diagnosis and treatment result in partial improvements.

In a previous study [1], low serum concentrations of folic acid were found in 86% of patients (6/7) with folic acid deficiency-induced myelopathy (mean reference range 0.6–1.0 ng/mL). In another study [4], serum copper concentrations were low in all 55 CDM patients examined (mean reference range 0.0–70 μg/dL), and were below 10 μg/dL in 45% of cases (n = 25). Although our patient had both folic acid and copper deficiency, his serum folic acid and copper concentrations were not as low as those reported previously. Synergic effects between the copper and folic acid deficiency may have caused our patient's spinal cord injury, however, further examinations are required to verify such synergic effects. Winston and Jaiser [6] suggested that methylation cycle dysfunction was the common cause of spinal cord injury in CDM and SACD. Because methionine synthase in the methylation cycle is dependent on both copper and cobalamin, dysfunction of methionine synthase may contribute to myelin injury in the spinal cord [6]. Recent reports have demonstrated that DNA methylation is critical for regulating the proliferation and differentiation of oligodendrocytes [7]. Thus, in the present case, a deficiency in both copper and folic acid may have

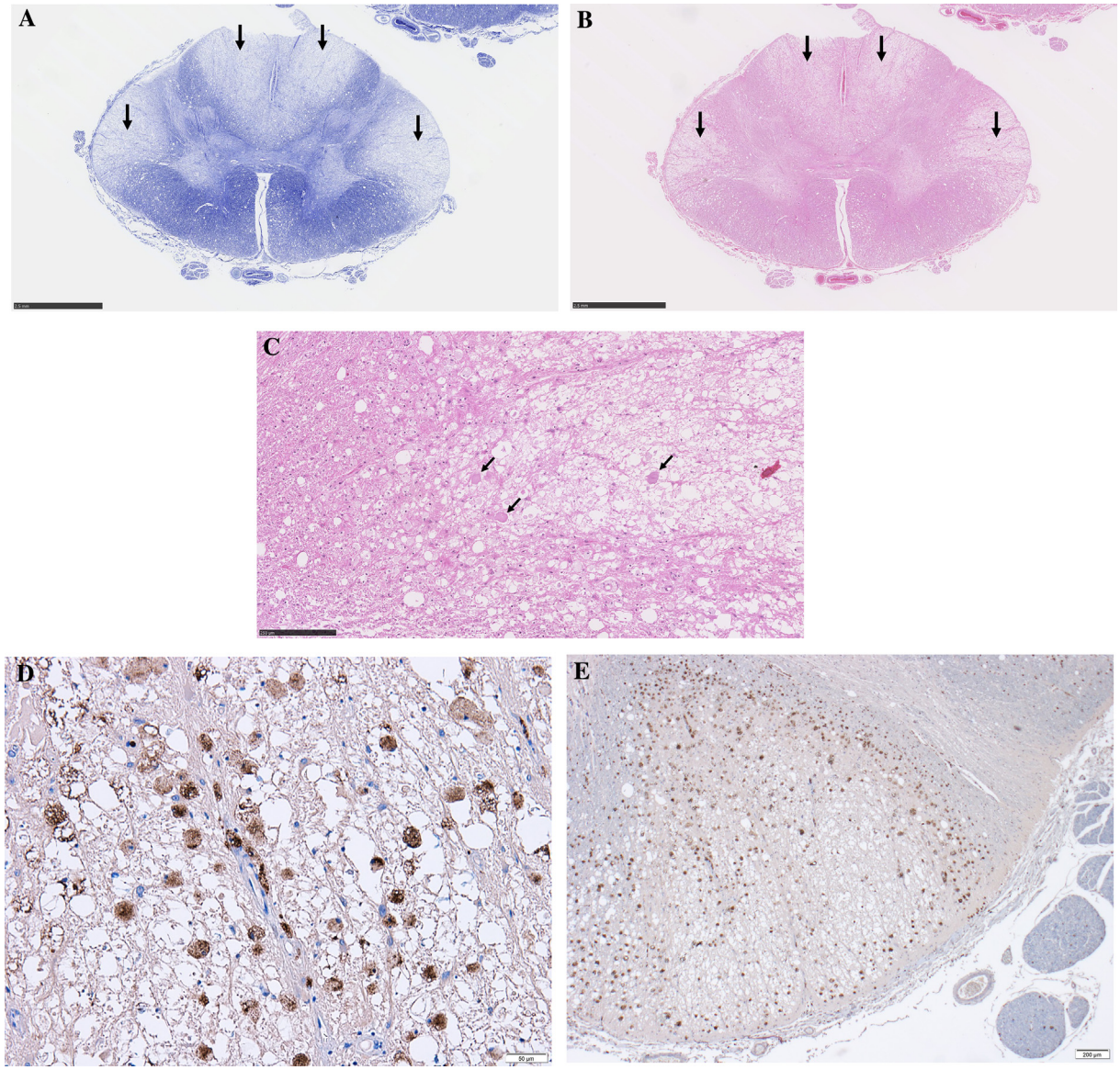


Fig. 2. Autopsy findings. The myelin in the posterior and lateral columns of Th7–12 was not stained with either (A) luxol fast blue or (B) hematoxylin and eosin (HE) (*black arrows*). In the demyelinated lesion, anti-CD68 antibody stained microglia/macrophage infiltrated). Neither astroglia nor lymphoblasts were observed (C: HE, D, E: anti-CD68 antibody immunohistochemistry). Axonal spheroids, which indicate axonal damage, were observed in the lesion (C, *black arrows*).

resulted in dysfunction of the methylation cycle, which resulted in spinal cord demyelination.

The antitumor drug MTX, a folate antagonist, is used for the treatment of hematological tumors and is known to cause myelopathy, such as SACD [3]. MTX myelopathy is treated by discontinuing MTX and providing folic acid supplementation. However, MTX myelopathy is resistant to therapy, and has a poor prognosis.

NEL-induced myelopathy was also suspected in the present case, but the interval period from administration of NEL to the onset of myelopathy symptom was for five months, which is much longer than those in the past reports, several days to two months [8,9]. Furthermore, in SACD, both posterior and lateral spinal column are injured, whereas only posterior spinal column lesions have been reported in NEL-induced myelopathy [8,9]. Thus, although the influence of NEL cannot be completely ruled out, this case is not likely to NEL-induced myelopathy.

MRI findings in SACD can greatly help with diagnosis. Symmetrical $T_2$ signal hyperintensities in the posterior and lateral spinal cord, and rarely the brainstem, are very typical MRI findings [10]. In our patient, spinal MRI revealed the same symmetrical $T_2$ signal hyperintensities in the posterior and lateral spinal cord. Although there are different causes of SACD (e.g. vitamin $B_{12}$ deficiency, copper deficiency, and folic acid defi-

ciency), these MRI findings have been reported in all types of SACD, except for that caused by folic acid deficiency [2].

Our patient suddenly suffered from cardiopulmonary arrest (CPA). Acute adrenal insufficiency was suspected as a cause of death, because the patient had been decreased steroids before CPA, serum cortisol level was low (1.3 μg/dL) at CPA, and hyponatremia and hyperkalemia were observed. Pathological findings also showed thinning of the adrenal gland, which supported the diagnosis of clinical acute adrenal insufficiency.

Autopsy cases of childhood or adolescent SACD patients are very rare, with one report in a 2-year-old girl with 5,10-methylenetetrahydrofolate reductase deficiency [11] and another in a 23-year-old woman with Down syndrome with MTX-induced myelopathy [12]. In both cases, folic acid deficiency contributed to the pathogenesis. The present report is the first autopsy case report of SACD with folic acid and copper deficiency in an adolescent. Similar to previous reports, we found pathological evidence of SACD showing demyelination, in accordance with T2WI MRI findings of high-intensity lesions.

## 5. Conclusion

This case report is the first of an SACD patient with both folic acid and copper deficiency. Spinal MRI findings and microscopic findings were characteristic of SACD. Because SACD is usually reversible with early treatment, it should be suspected in a high-risk patient undergoing chemotherapy or with malnutrition showing characteristic symptoms of SACD, even in young patients.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.07.006.

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