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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spinal muscular atrophy and acute lymphoblastic leukemia – is it just a coincidence?

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SUMMARY

Introduction Spinal muscular atrophy (SMA) and acute lymphoblastic leukemia (ALL) are rare diseases, with usual onset in childhood. To date, no cases have been reported where these conditions co-exist in one patient. Nusinersen has not been used concurrently with chemotherapy for ALL in children. The aim of the paper is to present two patients with two rare diseases and the results of their therapy.

Outlines of cases We describe two patients diagnosed with SMA and ALL. The first patient received nusinersen, while the second did not receive SMA treatment. ALL in both patients was successfully cured by the appropriate treatment protocol. In the first patient, nusinersen was temporarily discontinued but restarted during the maintenance phase of chemotherapy. The chemotherapy regimen in the first patient was modified during the maintenance of ALL treatment.

Conclusion The concomitant use of nusinersen and chemotherapy for ALL in our first case was safe, demonstrating good efficacy and tolerance without significant interactions or adverse events. We consider the occurrence of ALL and SMA in our both patients to be just coincidental; however, further research is needed to clarify many dilemmas about potential connections between these two rare diseases.

Keywords: rare disease; nusinersen; chemotherapy; concomitant

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare neurodegenerative disorder characterized by progressive muscular weakness and hypotonia. It is caused by the homozygous deletion of the survival motor neuron 1 gene (SMN1), leading to the degeneration of alpha motor neurons in the spinal cord. The incidence of SMA is approximately 1 in 6000 to11,000, but the carrier frequency is much higher [1, 2].

Until recently, SMA had a devastating prognosis. A new therapeutic era began when the first SMA treatment, nusinersen, was approved. [3]. Administered intrathecally, nusinersen targets the *SMN2* gene, resulting in increased production of SMN proteins. It has shown efficacy, improving global motor function and quality of life [4].

Acute lymphoblastic leukemia (ALL) is the most prevalent malignant disease in childhood [5]. The incidence of ALL ranged from 1–2 per 100,000 [6]. Despite being the most common malignancy in childhood, ALL remains a rare condition.

This paper presents two patients diagnosed with two rare diseases – SMA and ALL – as an unusual comorbidity, as well as the results of their therapy. In our cases, neither disease significantly influenced the clinical course of the other.

REPORTS OF CASES

Case 1

Our first patient was a four-year-old girl who was diagnosed with SMA type 2 at three months of age, with three copies of the *SMN2* gene. The diagnosis had been suspected prenatally due to a positive chorionic villus test. At the time of diagnosis, she was asymptomatic, and neurological examinations were normal.

The first clinical symptoms became observable at seven months of age, presenting as moderate hypotonia, weakness, and areflexia. She achieved independent sitting at nine months of age, but there was no further improvement. The initial CHOP-INTEND score was 44/64. The HINE score was 4/26. Other pediatric examinations and blood tests were normal, with no respiratory complications. Over time, moderate disease progression was observed consistent with the natural course of the disease.

Nusinersen was started at the age of two years and two months according to a standard protocol. After the fourth dose, a mild motor improvement was observed. All laboratory tests had been normal over time. However, 1.5 months after the fourth dose of nusinersen, she began to feel sick, with poor appetite, pallor, and anorexia. The blood samples revealed anemia (hemoglobin 3.1 g/dL) and thrombocytopenia (17,000/mm^3). The bone marrow aspiration showed 95% L1-type lymphoblasts,

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and B-cell ALL was diagnosed, with no central nervous system involvement (CNS stage 1) [6]. All genetic tests were normal without any common genetic mutations (e.g., Bcr/Abl, MLL/AF4, PBX1/E2A gene fusions etc.) [7].

ALL therapy was immediately started according to IC-BFM 2009 protocol [six-month induction phase of chemotherapy, followed by a maintenance phase including four intrathecal methotrexate (MTX) doses] [8], while nusinersen was discontinued. Complete remission established on the 33rd day, classified into the intermediate-risk group [9]. Consequently, ALL treatment continued with the IC-BFM 2002 protocol for the next 23 months.

Four months after the beginning of the maintenance phase of ALL therapy and 13 months after the last dose of nusinersen, the SMA therapy was continued. Regarding to ALL therapy, slight modifications were made to the MTX regimen in the maintenance phase, with the reduction of two intrathecal MTX doses (administered on the fourth and 20th weeks instead of the fourth, eighth, 12th and 16th weeks of the maintenance phase).

Despite the successive administration of two different drugs through the same route and the modification to the MTX regimen, our patient did not experience significant adverse effects and drug interactions. No significant SMA progression was observed during ALL therapy, and the results of the follow-up motor tests were almost identical to the previous ones (12/26 *vs*. 13/26 in the HINE test).

Case 2

Our second case is a 20-year-old woman diagnosed with SMA type 3 at 20 months of age with three copies of the *SMN2* gene. The first clinical symptoms appeared at 18 months of age, after she had started walking. She did not receive any causal SMA therapy due to the unavailability of treatment at that time. Clinical progression followed the natural course of the disease, and she lost the ability to walk by six years of age.

At the age of four years, she began to feel unwell, tired, apathetic, and pale. The complete blood count revealed anemia (hemoglobin 8.7 g/dL) and thrombocytopenia (60,000/mm^3), raising suspicion of malignant blood disease. The results of bone marrow aspiration showed 97% L1-type lymphoblasts, leading to a diagnosis of pre-B type ALL with no central nervous system involvement (CNS 1) [6]. The standard ALL treatment according to the ALL IC-BFM 2002 protocol was initiated, and complete remission was achieved on the 33rd day of treatment. Classified as an intermediate-risk group [9], she continued treatment according to the same ALL protocol for the remaining 23 months.

Despite the concurrent SMA, our patient showed a favorable clinical response to ALL therapy and did not experience any unexpected adverse effects related to SMA. The course of SMA followed its natural progression without any unexpected deterioration due to ALL.

All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

We present two patients diagnosed with two rare diseases – SMA and ALL. SMA in the first patient treated with nusinersen, while the second did not receive any SMA treatment due to the unavailability of specific therapy at the time. ALL in both patients was successfully treated according to the appropriate treatment protocol [10]. In the first patient, simultaneous therapy with nusinersen and chemotherapy demonstrated good efficacy and tolerance, with no interactions or significant adverse events. This paper may serve as an example of a clinical approach for managing ALL in children with SMA treated with nusinersen.

The question arises: is there a relationship between the two diseases – genetic, geographical, or environmental – or are they merely coincidental? To the best of our knowledge, we did not find any observable direct or indirect association in the occurrence, development, and course of these two rare diseases. SMA is a rare autosomal recessive monogenic disease caused by biallelic mutations – deletion in the *SMN1* gene located on the 5q13 chromosome in 95% of cases. In less than 5% of cases, it may be caused by a heterozygous mutation of the *SMN1* gene associated with a point mutation on the other *SMN1* allele [2]. ALL is an acute sporadic malignant disease of the blood characterized by abnormal proliferation of the malignant immature B- or T-cells of the blood. Its etiology is unknown and involves multifactorial influences, including environmental and genetic factors such as translocations (e.g., t(1;19) [TCF3-PBX1], t(12;21) [ETV6-RUNX1], t(9;22) [BCR-ABL1]), MLL rearrangements, hypo/hyperdiploidy, intrachromosomal amplification of chromosome 21, mutations of the *JAK2* gene [11, 12, 13].

According to the literature, there is limited information regarding chromosome 5 abnormalities in the context of B-cell ALL. Trisomy of chromosome 5 has been reported in some cases B- or T-cell ALL and now presents one of the cytogenetic subgroups of ALL in the pediatric population with a poor prognosis [14]. Deletion of the long arm of chromosome 5 (5q) has been observed in myelodysplastic syndromes (10–15%) and acute myeloid leukemia, and rarely in T-cell ALL in both adults and children, but not in B-cell leukemia [15]. Among the rare cases reporting chromosome 5 abnormalities in ALL patients, none have 5q13 abnormalities, which is a significant gene locus for SMA occurrence [16].

According to our best knowledge, this paper is the first presentation of two patients with both SMA and ALL. Although there have been a few reported cases of SMA co-occurring with other malignancies, none of these patients were treated with nusinersen [17–21]. Yaris et al. [17] reported a case of a child with SMA and disseminated alveolar rhabdomyosarcoma. Three years later, Rudnik-Schöneborn et al. [18] described two cases of SMA type

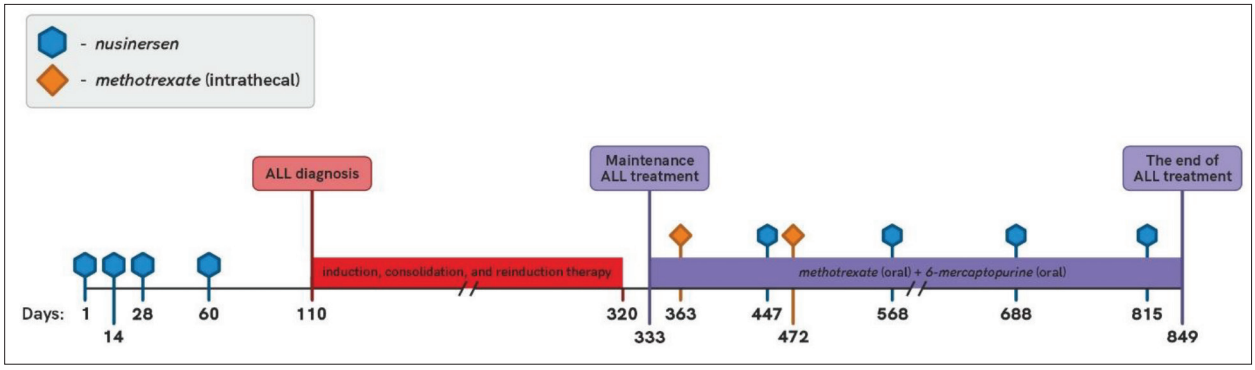

Figure 1. Schedule of spinal muscular and acute lymphoblastic leukemia (ALL) treatment in case presentation 1

II and IIIa associated with alveolar rhabdomyosarcoma, diagnosed at the age of 15 and 19 years, respectively. In 2015, Sag et al. [19] documented a four-month-old infant with SMA type 1 and neuroblastoma, while Blatt and Gold [20] reported a three-year-old diagnosed with stage-4 neuroblastoma, whose sister had SMA type 1. Additionally, there is one documented case of ependymoma in an adult female with SMA type 4 [21].

The revolution in SMA treatment and the availability of specific therapy for SMA raise several questions: Are there any connections between SMA therapy and the occurrence of ALL? How might SMA therapy influence ALL treatment, and vice versa? What are the implications of administering different medications through the same route? According to previous clinical studies, nusinersen, the first approved specific therapy for SMA for patients of all age groups, has proven to be effective, especially in presymptomatic patients, and is considered to be safe treatment as well. The adverse effects of nusinersen are generally mild and temporary [3, 4, 22]. Myotoxicity, a common adverse effect of chemotherapy, has not been reported as a side effect of nusinersen, although it can lead to mild thrombocytopenia. Besides mild changes in urine protein levels, nusinersen does not significantly change other laboratory parameters [23, 24].

Considering the well-known adverse effects of chemotherapy, we had several concerns about the simultaneous use of nusinersen and ALL therapy in our first patient, especially considering the same route of administration for nusinersen and MTX [25]. According to literature on the pharmacokinetics, nusinersen has demonstrated minimal drug-to-drug interactions. Intrathecal administration of nusinersen results in low plasma concentration, with minimal impact on peripheral tissues, blood, and the CYP450 system in the liver [26]. Given this consideration, we anticipated no significant interactions between nusinersen and chemotherapy in our patient. However, due to limited knowledge regarding the concurrent use of these medications, we temporarily discontinue nusinersen during the induction phase of ALL treatment and restart it during the maintenance phase, when the ALL treatment regimen is less intense. We resumed nusinersen four months after the initiation of the maintenance phase of ALL therapy. Despite the significant interval between nusinersen doses (almost 13 months between the fourth and fifth dose), we opted to continue nusinersen according to the standard maintenance protocol every four months. In addition, we modified the intrathecal MTX schedule during the maintenance phase of ALL therapy to mitigate potential interactions between nusinersen and intrathecal MTX, and to reduce the frequency of lumbar punctures. Throughout the maintenance phase, our patient received four doses of nusinersen and two doses of MTX intrathecally, with at least one-month interval between nusinersen and MTX (Figure 1). Our patient did not experience adverse effects or interactions from either therapy [3, 4, 26].

Finally, we question whether nusinersen has had any impact on carcinogenesis in our first patient. Preclinical studies have suggested that subcutaneous nusinersen administration in mouse models could increase the risk of vascular tumors [26]. However, according to current references, there is no evidence suggesting that nusinersen influences the development of other malignancies. To the best of our knowledge, we do not believe nusinersen affected malignancy in our patient; nevertheless, further research is needed to resolves these concerns.

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Conflict of interest: None declared.

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Спинална мишићна атрофија и акутна лимфобластна леукемија – да ли је само случајност?

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САЖЕТАК

Увод Спинална мишићна атрофија (СМА) и акутна лимфобластна леукемија (АЛЛ) ретке су болести које се обично јављају у детињству. До сада није забележено да ове две болести коегзистирају код једног болесника. Нусинерсен још увек није примењен у комбинацији са хемиотерапијом код деце.

Циљ овог рада је да представи два болесника са две ретке болести, као и резултате њиховог лечења.

Приказ болесникâ Приказујемо два болесника код којих је дијагностикована СМА и АЛЛ. Први болесник је примао нусинерсен, док други болесник није добио ниједну СМА модификујућу терапију. АЛЛ је код оба болесника успешно излечена помоћу одговарајућих терапијских протокола. Код првог болесника нусинерсен је привремено обустављен, али је поново уведен током фазе одржавања. Протокол лечења АЛЛ је модификован током фазе одржавања.

Закључак Код првог болесника истовремена примена нусинерсена и хемиотерапије била је сигурна, ефикасна и добро толерисана, без значајних интерреакција и нежељених ефеката. Сматрамо да је појава АЛЛ и СМА код наших болесника случајна; међутим, потребна су даља истраживања како би се разјасниле дилеме о могућим везама између ове две ретке болести.

Кључне речи: ретке болести; нусинерсен; хемиотерапија; истовремено