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# Nodal form of Rosai-Dorfman-Destombes disease

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Lymphadenopathy is a condition in which the lymph nodes are abnormal in size and consistency [1]. These abnormal nodes can also be characterized by immobility in relation to surrounding tissues, uneven surface, changed skin above them, or the formation of bundles [2]. Cervical lymphadenopathy can affect 90% of children between the ages of 4 and 8, and is one of the most common reasons for children to be referred to oncohematology centers by family doctors [3]. Generally, a lymph node is considered to be enlarged when its largest dimension exceeds 10 mm, with the exception of supraclavicular, popliteal and supratrochlear (elbow) nodes, where the limit is 5 mm, and inguinal nodes which normally do not exceed 15 mm [1, 2]. Depending on the number of sites of enlarged lymph nodes, two types of lymphadenopathy are distinguished: localized, affecting a single node group, and generalized, involving at least three non-adjacent groups of nodes [1, 2]. Local lymphadenopathy is much more common than generalized [1].

The main causes of lymphadenopathy are infections with viruses, bacteria, and other microorganisms, as well as caries, periodontal disease, Kawasaki disease and malignancies including histiocytosis [3]. In most cases, a thorough patient history and physical examination make it possible to determine the cause of lymphadenopathy [1, 3]. It is important to pay attention to the general symptoms i.e. fever, night sweats, weight loss (>10% of body weight within 6 months), joint pain, and muscle weakness [1]. Diagnosis for proliferative disease is required in children with rapidly enlarging cervical nodes in the absence of infection symptoms, enlargement of nodes >20 mm for more than 6 weeks, and palpable nodes in the supraclavicular region [3]. Ultrasonography is indicated in children with an uncertain diagnosis and those who do not respond to empirical treatment [3]. The gold standard diagnosis is an open biopsy, which consists in removing the entire node in order to preserve its architecture [3]. Fine-needle biopsy in children is contraindicated because it is unreliable [1].

We present the case of a 2-year-old boy diagnosed with right cervical lymph nodes enlargement after upper respiratory tract infection with low-grade fever (Figure 1). Amoxicillin with clavulanic acid followed by cefuroxime were used, with insignificant improvement. After two months, during gastroenteritis, right cervical lymphadenopathy recurred. Amoxicillin with clavulanic acid followed by clarithromycin were used, but with no improvement. In physical examination, a 4 cm in diameter movable bundle of lymph nodes with no skin change on the right side of the neck below the jaw was palpable. Blood cell count, lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein and uric acid were within normal ranges. No serological evidence of fresh infection of toxoplasmosis, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus HCV, cytomegalovirus (CMV), Epstein-Bárr virus (EBV) or cat scare disease

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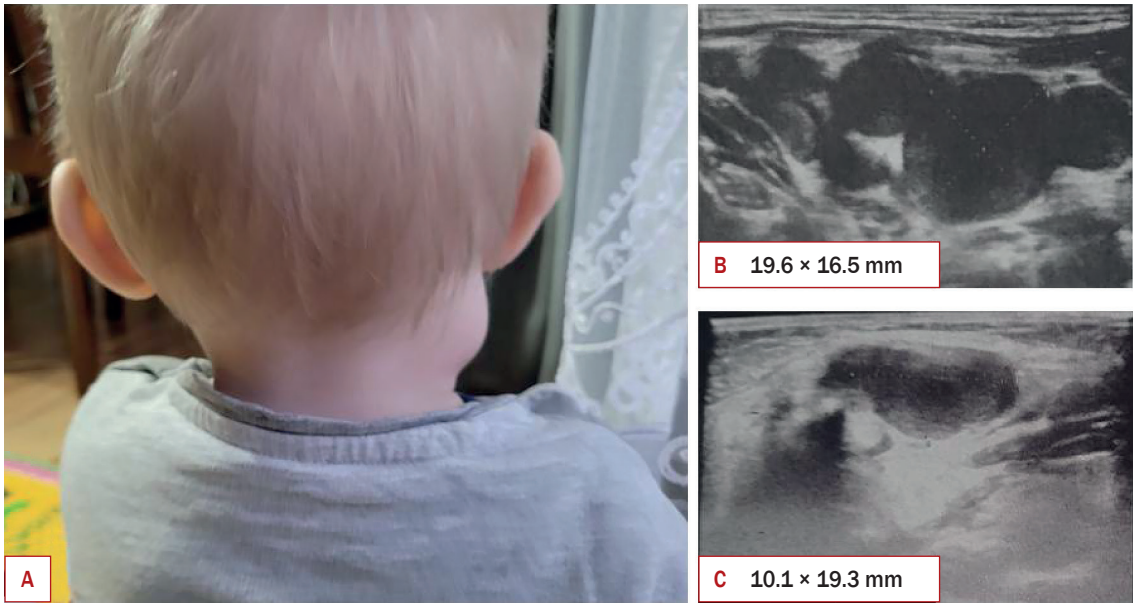


**Figure 1.** Manifestation of lymphadenopathy: in clinical examination (**A**), ultrasonography of right cervical lymph nodes (**B**) and right submandibular lymph nodes (**C**)

was present. No abnormalities were found in chest X-ray or abdominal ultrasound. In lymph nodes ultrasonography, a few enlarged submandibular and cervical lymph nodes up to 31 × 14 mm with visible sinuses and features of increased, retro-sinusoidal vascular flow were present. Open biopsy of right cervical and submandibular lymph nodes was performed. In the histopathological examination, histiocytes in the dilated sinuses showed the presence of S-100 and CD 68/PGM1 proteins, with a negative reaction for CD1a. A histopathological diagnosis of Rosai-Dorfman-Destombes disease (RDD) was made. Next-generation sequencing did not reveal *BRAF, NRAS,* or *KRAS* mutations. After the staging, the unifocal nodal form of RDD disease was diagnosed. An observational strategy was applied with no other systemic or local treatment. After 18 months of follow-up, the patient is in remission with no symptoms of the disease.

Histiocytoses form a large group of diseases, the essence of which is the clonal proliferation and accumulation of cells derived from macrophages, monocytes and dendritic cells in various tissues [4]. Histiocytosis is a very rare disease, diagnosed in Poland in about 20–30 children a year [5], while RDD disease is a sub-type of histiocytosis where patients manifest massive lymphadenopathy and sinus histiocytosis in histological analysis [6, 7]. RDD affects monocytes and macrophages, occurs in children and young adults [4, 8–10], and is more common in males than in females [7–10]. Its etiology is unknown, but one theory is that human herpesvirus (HHV)-6, HHV-8, parvovirus B19, EBV, CMV, and varicella zoster virus (VZV) may be potential causative agents [8]. Histiocytes are S100, CD68 positive and CD1a negative in immunohistochemical examination [7–9]. Some studies have identified *KRAS*, *NRAS*, *ARAF* and *MAP2K1* mutations [6, 7]. Classic nodal, and extranodal, types are distinguished [6, 7]. In most cases of classic nodal form of RDD, the patient will present with bilateral, massive, painless cervical lymphadenopathy with or without intermittent fever, night sweats and weight loss [6–8]. Mediastinal, axillary, inguinal nodes also may be involved, but retroperitoneal lymphadenopathy is uncommon [7].

Extranodal disease is seen in over 40% of cases predominantly in the head and neck region [8, 10] including the skin, nasal cavity, orbital tissue and central nervous system [6–8, 10]. Although bone marrow infiltrations are rare, hematological abnormalities have been observed [7]. RDD is mostly a self-limiting disease [10] with up to 50% of cases resulting in spontaneous remission [6, 8]. If the newly diagnosed disease is stable, without progression, an observational approach should be adopted [6, 7]. Surgery is usually limited to biopsy, but resection can be curative for unifocal disease [7]. In the case of generalized changes, systemic therapy with corticosteroids, sirolimus, radiotherapy, chemotherapy and immunomodulatory therapy is used in the treatment [6–8]. In November 2022, the U.S. Food and Drug Administration (FDA) approved cobimetinib (an oral MEK inhibitor) for the treatment of adult patients with RDD [11].

In conclusion, this case illustrates a simple cervical lymphadenopathy as a symptom of a very rare disease, even in a very young child. Diagnostic biopsy can also be a curative therapy for RDD, while an observational strategy should be applied in focal stages of this disease.

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## Authors' contributions

KC, OG — design of study; OG, KJ, AM, PG, JS, KC — provision of clinical data; ML — molecular testing and analysis; OG, KC — literature search and analysis of data; OG, KC — writing manuscript. All authors — analysis of clinical data, critical revision, and final approval.

## Conflict of interest

The authors declare no conflict of interest.

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## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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