

Reviewer #1:

General comments: this case report is presented in a concise and clear way and is well documented with good clinical, radiological and histological figures. The teaching point of the case is that diagnosis is done by histological analysis and cannot be done by imaging techniques, which the authors state in the conclusions. The outcome of the patient is not mentioned in the article and needs to be added, especially regarding the lung lesions, in order to add evidence that the lung nodules are indeed Rosai-Dorfman disease related. The main differential diagnosis (Langerhans cell histiocytosis) was ruled out by immunohistochemistry. Specific points:

Comment 1: where infectious diseases (e.g. mycobacterial infection) ruled out? If not, rule out with appropriate stains, if yes, add a sentence clarifying this point.

Response: We are glad to accept the suggestion.

Firstly, the patient had Mycobacterium tuberculosis nucleic acid test; the result showed negative. Also, in the culture of wound secretion, we did not find acid-fast bacilli or fungi were found.

Secondly, in this case, the patient had multiple pulmonary nodules, but no clinical symptoms such as cough, expectoration, hemoptysis, low fever, and chest pain. The CT image was inconsistent with the image of pulmonary tuberculosis infection. The pathological manifestation, in this case, was typical; immunohistochemistry revealed positivity for CD68, CD163, and S100, indicating the possibility of RDD with lung involvement.

Thirdly, based on the clinical symptoms, test results, and CT image, we considered it was not mycobacterial infectious diseases. However, we admit that we did not do further examinations to exclude mycobacterial infection. This may become a limitation of this case. Thus, we are planning to do related works in our future study.

Finally, in the revised article, test results and analysis have been added.

"Mycobacterium tuberculosis nucleic acid test showed negative. In the culture of wound secretion, no acid-fast bacilli and fungi were found, but Gram-positive cocci were found and sensitive to clindamycin." (please see line 106, page 4)

"In this case, the patient had multiple pulmonary nodules, but no clinical symptoms such as cough, expectoration, hemoptysis, low fever, and chest pain. The CT image was inconsistent with the image of pulmonary tuberculosis infection. The pathological manifestation, in this case, was typical; immunohistochemistry revealed positivity for CD68, CD163, and S100, indicating the possibility of RDD with lung involvement. However, no further examination to exclude Mycobacterium infection was the limitation of this case." (please see line 182, page 7)

Comment 2: How do the authors explain the clinical picture with ulceration of the skin? Superinfection? Cutaneous involvement? This is an unusual clinical presentation.

Response: We are glad to accept your suggestion.

Firstly, the patient underwent surgery in another hospital. It was more likely that the patient had poor skin healing after the surgery.

Secondly, the skin of children was delicate. An increase of the tumor oppressed the skin. This affected the local blood supply and led to inflammation. These led to skin damage.

Thirdly, the patient and her family member had improper nursing care. The improper care led to infection and procrastination.

Fourthly, the nature of the tumor had not been clear for a long time. Thus, no effective treatment was taken to control the tumor.

Fifthly, we considered that the above four analyses led to ulceration of the skin.

Finally, we have added analysis in the revised article:

"Concerning skin ulcers, we have the following considerations: first, before the onset of this disease, the patient had undergone surgery in other hospitals, and there was the possibility of poor local skin healing; secondly, the skin of children was delicate, and the tumor continued to increase and oppress, affecting the local blood supply and leading to inflammation, which were all factors of skin damage. Thirdly, improper nursing care for family members and the patient after skin damage led to infection and procrastination. Finally, the nature of the tumor had not been clear for a long time, and there was no effective treatment to control the disease. These causes lead to ulceration of the skin, an unusual clinical presentation." (please see line 190, page 7)

Comment 3: add a paragraph on follow up of the patient, what treatments were administered and how was the outcome. This is especially important to add evidence that the lung nodules are Rosai Dorfman disease (i.e. if they regressed together with the lymph node lesions).

Response: Thank you for your comment.

Firstly, the follow-up results showed that the cervical lymph nodes and pulmonary nodules were enlarged at the same time. Thus, we considered that both lesions were caused by RDD.

Secondly, the enlargement of the cervical lymph nodes and pulmonary nodules suggests that the treatment was not sufficient. Thus, we are planning to change the treatments and keep following up on this case.

Finally, we have added details in the revised article:

"There were skin ulcers in the left neck, accompanied by purulent secretions, considering local infection, empiric intravenous antibiotic therapy for 9 days with Cefmetazole sodium 1 g bid. After gram-positive cocci and drug sensitivity test was found in wound secretion culture, Cefmetazole sodium was stopped and intravenous Clindamycin hydrochloride injection 0.15g bid was used for 7 days. According to the pathological and immunohistochemical results of lymph nodes, RDD was diagnosed. The patient was discharged from the hospital after the operation recovered well, and was treated with 75 mg of clindamycin palmitate dispersible tablets 3 times a day for 1 week and prednisone acetate 15mg once a day for one week followed by 5mg once a day for 6 weeks." (please see line 133, page 5)

"The patients were followed up 9 months later (February 2021). The ulcer in the left neck was better than before, and no purulent secretion was found (Figure6). CT showed that the bilateral pulmonary nodules were significantly increased and enlarged. The largest nodule was located in the right lower lung with a diameter of about 3.3cm (Figure7). Neck MRI showed multiple round-like soft tissue masses of different sizes in the left parapharyngeal space, carotid sheath area, submandibular region, cervical root, supraclavicular fossa, and supraclavicular region. Most of the lesions were fused into masses (the largest was 6.9 cm × 9.0 cm × 12 cm), with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Figure8). With the consideration of current poor control of the disease, the doctor advised the patient to be hospitalized again. The patient's family said they needed to consider it." (please see line 145, page 5)

"The follow-up results showed that the cervical lymph nodes and pulmonary nodules were enlarged at the same time, considering that both lesions were caused by RDD. At present, the cervical lymph nodes and pulmonary nodules were further enlarged and increased, considering

the poor treatment control and the need to change the treatment plan, we will continue to follow up on this medical record.” (please see line 200, page 7)



Figure6: (please see line 308, page 13)

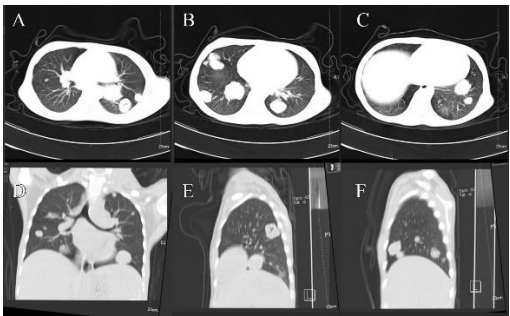


Figure7: (please see line 311, page 13)

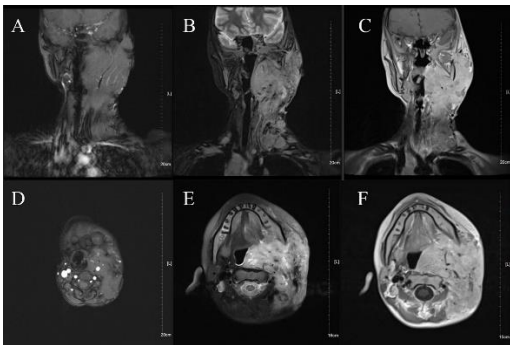


Figure8: (please see line 316, page 14)

Comment 4: since the paper is published in english, replace references in other languages (whenever possible) with english literature, in order to allow all readers to read referenced work (i.e. References 6, 8, 10, 12, 13)

Response: We are glad to accept the suggestion. We changed the referenced work in the revised article (i.e. Reference 6, 8, 10, 12, 13)

“the disease has a slight male predilection, with a male/female ratio of 3:1 and more frequently affects males of African descent.” (please see line 68, page 3)

“The main treatments for RDD include observation, surgery, corticosteroids, sirolimus, chemotherapy, immunomodulatory therapy, targeted therapies, radiotherapy, but no uniform approach has been delineated for RDD, and treatment is best tailored to the individual clinical circumstances.” (please see line 74, page 3)

"Raslan et al. reported that the affected lymph nodes were homogeneously enhancing and might show central hypodensity on CT. MRI characteristics of the involved areas are generally T1 isointensity, T2 isointensity, and intense enhancement with gadolinium agents. PET shows variable uptake.¹²" (please see line 162, page 6)

"the diagnosis of RDD depends on the histopathology.¹³" (please see line 166, page 6)

Comment 5: The abstract needs some editing: summarize the radiological findings, "S100" and not "Smur100" and need some grammar editing.

Response: We make an apology for our carelessness.

Firstly, we have added a summary of the radiological findings in the abstract.

"The cervical MRI showed multiple masses in the left neck, with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, considered as a malignant tumor, with a high possibility of lymph node metastasis. At the same time, lung CT showed multiple nodules of different sizes scattered on both sides of the lung, the internal density was uniform and considered it is a possible metastatic tumor." (please see line 32, page 2)

Secondly, "S100" has been used instead of "Smur100".

Finally, the authors have carefully examined the grammar in the whole article.

Comment 6: core tip: rephrase, as currently it is just a repetition of the abstract. What is the core message of this case report?

Response: We are glad to accept your suggestion.

The core tip has been revised as follows:

"This case shows that in a 10-year-old female characterized by enlarged left cervical lymph nodes, imaging revealed a malignant tumor with pulmonary metastasis, and Rosai-Dorfman disease (RDD) was finally diagnosed by pathological and immunohistochemical methods. This case suggests that we should pay attention to RDD in the differential diagnosis of cervical masses. Secondly, in the diagnosis of RDD, we should not rely solely on imaging examination, but to comprehensively consider the use of different diagnostic methods; moreover, although rare, there is a situation that RDD involves the lungs; finally, the treatment of RDD needs to be constantly explored and the treatment plan should be adjusted according to the follow-up results." (please see line 49, page 2)

Comment 7: avoid specific dates ("2018"), rather write "two months before/after" ;the disease has a slight male predilection, not "mainly occurring in males" (line 6 of main text) -remove "and so on" from list of treatment options -there are few grammatical mistakes/typos, such as "multriple", "found retrieved", "is that the extent"; Key words: "case report" is missing.

Response: We sincerely apologize for our carelessness. The authors have examined and revised the article carefully.

"two months before/after" has been used (please see line 85, page 3). "the disease has a slight male predilection" has been used (please see line 68, page 3). The author has removed "and so on". "case report" has been added in key words (please see line 48, page 2)

Comment 8: since the disease is mostly self-limited why is a long-term follow up needed? (last sentence)

Response: Thank you for your comment.

Firstly, although RDD has not been classified as a neoplastic disorder until now, recent evidence has that clonality in a subset of cases raises the possibility of a neoplastic process. And the treatment of RDD is a long-term exploratory process; RDD management requires adjustment according to the follow-up. Thus, we considered a long-term follow-up is needed.

Secondly, we have added details and a reference in the revised article as following:

"Although RDD has not yet been currently classified as a neoplastic disorder, recent evidence demonstrating clonality in a subset of cases raises the possibility of a neoplastic process.¹⁶ The treatment of RDD is a long-term exploratory process. RDD management requires timely adjustment of a treatment plan according to curative effect evaluation during follow-up." (please see line 211, page 8)

Reference 16. Bruce-Brand C, Schneider JW, Schubert P. Rosai-Dorfman disease: an overview. J Clin Pathol. 2020 Nov;73(11):697-705. [PMID: 32591351 DOI: 10.1136/jclinpath-2020-206733]

Reviewer #2:

Thank you for giving us the opportunity to evaluate this paper. The authors presented a case report of the rare Rosai-Dorfman disease in a 10-year-old boy with cervical lymphadenopathy and multiple nodules in the lungs. It is a well-written article overall. RDD is important because it is a rare disease and should be known in the differential diagnosis in patients with neck mass. However, the authors need to make some revisions.

Comment 9: In keywords, "cervical lymphadenopathy" and "neck mass" can be considered instead of RDD.

Response: Thank you for your comment. The authors have added the key words "cervical lymphadenopathy", "neck mass", and deleted the "RDD" (please see line 47, page 2).

Comment 10: Introduction In line 10, the phrase "..multiple extranodal" should change to ..multiple extranodal ...

Response: Thank you for your comment. 'multiple extranodal' has been changed to 'multiple extranodal' (please see line 74, page 3).

Comment 11: Case report In the first use of abbreviations such as MRI, CT, the full name should be written. T1 weighted imaging (WI) should be used instead of T-1WI. T2 weighted imaging should be used instead of T-2 WI. ``

Response: Thank you for your comment. The authors have added full names in the first use of abbreviations and carefully examined the whole article. Magnetic Resonance Imaging has been added before MRI (please see line 110, page 4). Computed Tomography has been added before CT (please see line 119, page 4). T1 weighted imaging (WI) has been used instead of T-1WI (please see line 114, page 4). T2 weighted imaging has been used instead of T-2 WI (please see line 114, page 4).

Comment 12: The largest nodule was located in the dorsal segment of the left lower lung with a diameter of approximately 1.2 cm " "Upper segment" should be used instead of "dorsal segment".

Response: Thank you for your comment. The authors have replaced with dorsal segment with upper segment (see line 120, page 5), and carefully examined the whole article.

Comment 13: Figures The full name of the MRI should be written in Figure 2. (magnetic resonance imaging) In Figure 3, "(b, c, d) abdominal ultrasound" should be written instead of "(b, c, d) Abdominal color ultrasound ...". In Figure 4, CT should be written with its full name.

Response: Thank you for your comment. The authors have added full names in the first use of abbreviations and carefully examined the whole article. Magnetic Resonance Imaging has been added before MRI in Figure 2 (please see line 288, page 11). "(b, c, d) abdominal ultrasound" has been used in Figure 3 (please see line 297, page 11). Computed Tomography has been added before CT in Figure 4 (please see line 302, page 12).