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Clinicopathologic Features Of Langerhans Cell Histiocytosis At Hasan Sadikin Hospital In 2010-2020

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ABSTRACT
Langerhans Cell Histiocytosis (LCH) is a rare neoplasm of myeloid origin, characterized by the proliferation of Langerhans cells expressing CD1a and CD207. While primarily affecting children, LCH can also occur in adults, though the incidence is extremely low. The disease manifests in various clinical forms, often complicating diagnosis and management. This study aims to describe the clinicopathological aspects of LCH cases treated at Hasan Sadikin Hospital (RSHS) Bandung over a ten-year period, from 2010 to 2020. Clinicopathological data of patients diagnosed with LCH at the Anatomical Pathology Department of Hasan Sadikin Hospital from 2010 to 2020 were retrospectively reviewed. Data collected included patient age, gender, anatomical location of the disease, and sampling methods used for diagnosis. Diagnosis of LCH was confirmed through morphological assessment of histopathologic specimens and fine needle aspiration biopsy (FNAB) smears. LCH remains a rare entity characterized by the abnormal proliferation of Langerhans cells, predominantly affecting children and most frequently involving the head region. Typical cytologic and histopathologic features are usually present, aiding in the diagnosis. However, variability in presentation underscores the importance of integrating clinical, radiologic, and immunohistochemical data for accurate diagnosis. Further research is warranted to explore long-term outcomes and optimal management strategies, particularly in regions with limited case data.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid cells characterized by positive expression of CD1a/CD207 on Langerhans cells. LCH is a rare disease in adults, with an incidence of only 1-2 per 1,000,000 cases (Tian, 2020). Most cases occur in children and can manifest clinically in various forms (Morimoto *et al.*, 2014). The disease is also known as abnormal proliferation of Langerhans cells, which can accumulate in various organs of the body. Previously, the nomenclature of LCH was often confusing because its naming was based on variations in clinical manifestations, with other names such as histiocytosis X or

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eosinophilic granuloma (Satter and High, 2008). The most commonly affected sites are the bones of the skull, femur, mandible, pelvis, and spina (Gong *et al.*, 2010).

In Luciana and Rusyati (2016) study, there was one case of Langerhans cell histiocytosis in a child aged 2 years and 4 months involving multisystem organs, which was difficult to diagnose because it was highly variable and resembled other diseases. The prognosis of multisystem HSL shows poor results, and if not treated properly, this condition can lead to a low life expectancy.

The Lurdes and Ariawati (2017) study indicates that it is important for each patient who shows signs of jaundice while visiting a pediatric clinic to investigate whether liver involvement in LCH is a potential cause. Jaundice can serve as an initial clinical sign of liver illness in LCH and can provide a hint towards the diagnosis. Timely identification and suitable therapy will result in improved results. This study aims to describe the clinicopathological characteristics of LCH cases diagnosed at Hasan Sadikin Hospital (RSHS) Bandung over a ten-year period, with a focus on identifying common presentation patterns and diagnostic features.

METHODS

The Anatomical Pathology Department of Hasan Sadikin Hospital Bandung provided clinicopathology patient data from 2010 to 2020. The data collected included age, gender, location, and sampling method. Patient data with LCH conclusions based on morphological assessment of LCH images histopathologically and from fine needle aspiration biopsy smears.

RESULTS AND DISCUSSION

The data shows that there were 33 patients from 2010 to 2020, with the highest number occurring in 2015 and 2017. The highest age range is between 1 and 10 years, namely 21. The most common location is the head with 10 cases, followed by the back and lymph nodes with 9 and 7 cases, respectively. The results of biopsy tissue sampling and fine needle aspiration biopsy smears guided the diagnosis. There were 11 female cases and 22 male cases. There were 23 unifocal cases, while the remaining 11 cases were multifocal. The microscopic picture of the fine needle biopsy smears revealed oval-round cells in 11 cases, pleomorphic nuclei in 3, coarse chromatin in 1, and granules in 2 cases. There were also inflammatory cell invasions of neutrophils in 2 cases, eosinophils in 3 cases, PMN in 1 case, lymphocytes in 3 cases, and multinucleated giant cells in 3 cases. Histopathological microscopic features discovered cells that were oval to round, differentiated Lengerhans cells in up to 16 cases, spindle cells in 1, monotonous cell nucleus in 3, reniform cells in 5, excess cells in 3, eosinophilic cells in 2, mitosis in 3, inflammatory lymphocytes in 12, PMN in 7, multinucleated cells in 6, eosinophils in 9, and plasma in 4. Six cases underwent fine needle biopsy with positive confirmation of CD1a and S100, and one case tested positive for CD68. In the histopathology preparations, immunohistochemical confirmation of CD1a and S100 was observed in one case each.

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Discussion

In this descriptive study, most were in the age range of 1–10. Gong et al.'s research supports the notion that LCH is more prevalent in childhood (Gong *et al.*, 2010). Similarly, Yağcı *et al.* (2008) research, which included 217 cases, found a median age of 3.5 years. This stands in stark contrast to the findings of Tian et al.'s research, which focused on adulthood (Tian, 2020).

Ten cases showed the head area as the most frequent location, with lymph nodes and the back following closely behind. In line with research conducted by Yağcı *et al.* (2008), who mentioned that the most common location is in the head area. The ratio of males to females affected by LCH is 2:1, not much different from the study of Yağcı *et al.* (2008), which obtained a ratio of 18:10.

The diagnosis of LCH is based on specific radiologic and/or pathologic features and immunohistochemical smears. Long bones can get osteolytic lesions in the metaphyseal area. These lesions have a mix of Langerhans cells, eosinophils, giant cells, neutrophils, foamy cells, and fibrosis areas. Immunohistochemical staining showed positive immunoexpression for CD1a and S100 protein-stained Langerhans cells.(Yağcı *et al.*, 2008). LCH can be unifocal or multifocal. This study only found eleven cases of multifocal LCH. Cases of multifocal LCH are rare. Shi *et al.* (2014) case report establishes multifocal LCH in the mandibular bone based on radiologic features and clinical data.

According to histopathology results, the microscopic features of LCH are round cells with a diameter of 12–15 micrometers and eosinophilic cytoplasm. The nucleus is irregular, with a clear fold in the center and fine chromatin, whereas the daughter nucleus is not clear. Often, one finds inflammatory cells such as lymphocytes, eosinophils, histiocytes, and neutrophils. In this study, the majority of cases displayed a typical microscopic appearance on histopathology. Only one case exhibited spindle-shaped cells in the histopathological picture, while the remaining cases displayed a typical picture along with a few additional accessories, enabling a differential diagnosis. This study heavily relied on immunohistochemistry.(Harmon and Brown, 2015)

The study's microscopic picture, especially of the skin, will show groups of cells just below the epidermis. These cells will have a large oval-round shape with irregular nuclei, a reniform nuclear groove, smooth chromatin, nuclei that aren't clear, and a lot of eosinophilic cytoplasm. Most of the cases found on the skin showed a proliferative pattern. In two cases, an ulcerative surface of the epidermis was found. Punia *et al.* (2006) case report, which discovered an ulcerative picture of LCH in the skin, supports this. The reaction pattern of LCH consists of 3 types, namely proliferative, granulomatous, and xanthomatous. In one case, there were many foamy macrophage images, according to the xanthomatous pattern. This pattern is relatively rare.(Punia *et al.*, 2006)

The microscopic picture of LCH cases in the skin is the standard for diagnosis, giving rise to many differential diagnoses (St. Claire *et al.*, 2020). There was also a mixture of inflammatory cells, including lymphocytes, neutrophils, and plasma cells. The microscopic image of the fine needle biopsy smear revealed an oval-round shape in 11 cases, a pleomorphic nucleus in 3, coarse chromatin in 1, and granules in 2. There were also

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inflammatory cell invasions of neutrophils in 2 cases, eosinophils in 3 cases, PMN in 1 case, lymphocytes in 3 cases, and multinucleated giant cells in 3 cases. According to Orell's textbook, the fine needle biopsy results reveal loose clusters of differentiated histiocytes with oval and round shapes, ranging in size from medium to large. The large nuclei are partially vesicular and partially indented, featuring irregular nuclear membranes. Mitosis is sometimes found; in some cases, there is no apparent cell division. Eosinophil inflammatory cells are often absent.

Some cases showed histiocyte-like cells, clustered with loose density but with pleomorphic nuclei. One section revealed histiocytes resembling the typical epithelioid cells seen in tuberculous inflammation. The inflammatory cells seen were scattered lymphocytes and neutrophils, with no eosinophils. In one case, we also found clusters of small to medium-sized oval-round cells with loose density, an irregular nuclear membrane, and smooth chromatin, some of which appeared vesicular. Scattered inflammatory cells included lymphocytes, neutrophils, and histiocytes. There are also clusters of cells with predominant fibrin and necrosis, complicating the assessment of cell morphology. This also makes for an atypical picture in LCH, especially in fine needle biopsy smear cytology preparations. A study by Hamda et al. also identified this type of fibrin and necrosis in one case.

In one case, there was a hypercellular picture filled with histiocyte-differentiated cells and multinucleated giant cells. One section revealed macrophage cells containing hemosiderin pigment. The image of hemosiderin-containing macrophages mirrors the findings of Handa *et al.* (2015) and the case study by Kumar, Sayed and Vinayak (2011). In a different case, the cytology showed that there were not many cells, with a lot of loose cells that had changed into histiocytes. These cells were mostly eosinophils and neutrophils, which are inflammatory cells.

In Hang, Siddiqui and Ali (2017) study of 37 cases, only 4 cases appeared hypocellular with a mixture of scattered inflammatory cells; only 1-2 Langerhans cells were found. Immunohistochemical pulses are necessary to make a diagnosis because the appearance of hypocellular cytology complicates the diagnosis (Hang, Siddiqui and Ali, 2017). Other cases revealed a dominant picture of Langerhans differentiated cells, characterized by round, oval cells ranging in size from medium to large, some loosely clustered and others scattered. The difference from other cases is the discovery of cells with pseudoinclusion and prominent daughter nuclei among loose groups of cells. Mixed inflammatory cells of lymphocytes, eosinophils, and plasma were also seen, but in relatively small numbers. This is similar to the case report submitted by Oza *et al.* (2015), who presented 3 rare cases, of which 2 cases showed a predominant Langerhans cell cytology picture, while the others were classified as predominant inflammatory cells.

The case report by Chandekar et al. also illustrates pseudoinclusion in the nucleus (Chandekar, Shah and Kavishwar, 2013). In one case, a generalized hypercellular picture was found consisting of loosely clustered and scattered histiocyte cell differentiation, an oval-round cell shape, partially eccentric nuclei with a few less significant indentations with some pseudoinclusion, and an and an irregular nuclear membrane. The daughter nuclei are partially prominent. Cytoplasm varies from scanty to abundant. Mixed inflammatory cells with

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predominant lymphocyte cells; no eosinophil inflammatory cells were found. There were also numerous multinucleated giant cells present. The case report presented by Shad et al. mentioned a similar picture to the one above, but the dominant inflammatory cells were eosinophils (Safa Al Shaikh *et al.*, 2017). Another case found LCH characteristics similar to the case above but with another variation, namely the infiltration of lymphocyte cells in the epidermis, also known as epidermotropism. A case report by Sun, Zhong and Chen (2016) also confirmed this.

The differential diagnosis of LCH includes histiocytic and dendritic lesions, as well as lymphoma. Both LCH and histiocytic and dendritic lesions display oval round cells with irregular nuclei, but distinguish themselves with eosinophilic cytoplasm. Additionally, LCH exhibits positive CD1a and S100 immunohistochemical expression. Both LCH and lymphoma share an oval round cell type, but in LCH, the histiocyte-differentiated oval round cells tend not to be diffuse or monotonous. The lymphoma IHK panel, which includes CD20, CD3, KI67, and positive IHK CD1a and S100 for LCH, distinguishes the immunohistochemical expression of both conditions (Harmon and Brown, 2015). Differential diagnosis is most common in fine-needle aspiration biopsy results.

Not only is there not a lot of clinical information available, but the lymph nodes that were found were mostly swollen, which is not a common finding. Also, the cytological features that were found were quite difficult and varied in one case preparation. It was very confusing. In some of the cases we talked about above, there were typical histiocyte-differentiated cells. In another section, there were also clusters of cells that looked like the epithelioid picture in tuberculous inflammation. The lack of eosinophil cells made us think that the tissue might be cancerous. Orell's textbook states that the absence of eosinophils, particularly in lymph node preparations, can lead to a multitude of differential diagnoses. If this is the case, further investigation in the form of S100 and Cd1a immunohistochemistry is absolutely necessary. In addition, the presence of this form of pseudoinclusion makes us think of another differential diagnosis, namely malignant melanoma or thyroid papillary carcinoma.(Chandekar, Shah and Kavishwar, 2013)

CONCLUSION

LCH is a rare case of myeloid proliferation, which involves Langerhans cells that accumulate in various organs. It is most common in children, especially in boys and on the head. In general, most cases present typical cytologic and histopathologic features, with only a small proportion having a spindle shape with coarse chromatin. Diagnosis is based on clinical data, radiologic features, histopathologic morphology, and immunohistochemistry.

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