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CUTANEOUS LYMPHANGIOMA CIRCUMSCRIPTUM SUCCESSFULLY TREATED WITH CRYOTHERAPY

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Abstract

Lymphangioma circumscriptum is superficial malformation, presenting as micro to macroscopic vesicles. It is often disfiguring and can negatively affect one's quality of life due to complications such as infection, and pain, making it of high value to elucidate current treatment options for the condition. High recurrence rates and a risk of scarring make lymphangioma circumscriptum difficult to treat. Treatment options for lymphangioma circumscriptum there are surgical excision, laser therapy, sclerotherapy, cryotherapy, radiotherapy, electrocautery, electrodessication and imiquimod in treating lymphangioma circumscriptum. In this case we treating lymphangioma circumscriptum using cryotherapy to minimal adverse effects.

Keywords: lymphangioma, cryotherapy, cystic tumor

Introduction

Cutaneous lymphangioma circumscriptum (CLC) is a rare congenital malformation of the superficial cutaneous lymphatic ducts, which manifests isolated or associated with deep lymphangioma or angiodysplastic syndromes. This lymphangioma is characterized by changes in the lymphatic structures with the formation of subcutaneous cisterns and ectopic vessels interconnected through dilated ducts that project into the skin in the form of superficial vesicles with thin walls and variable color.\textsuperscript{1-3}

A variety of treatment options for lymphangioma circumscriptum include surgery, sclerotherapy, cryotherapy, and lasers. Although these treatment options may yield positive results in some cases, relapses are often reported due to the deep placement of the lesions. Here, cases of cutaneous lymphangioma circumscriptum successfully treated with cryotherapy are presented.\textsuperscript{4,5}

Case

A 22-year-old female came to the dermatology outpatient clinic of Dr. Soetomo General Hospital Surabaya on March 06\textsuperscript{th} 2019. She came with
chief complaint of multiple vesicles on her right axillar. Her parents complained about it since she was 10 months old. Firstly, when she was 10 months old there are multiple vesicles in her right axillar. When she was 16 months old the multiple vesicles are surgically removed in Kediri Hospital, but when she was 10 years old vesicels reappear. In 2005 when she was 13 years old vesicels began to increase and more wide. In the last 2 years in 2017 clear liquid came out from vesicles cluster. Since 2018 clear liquid has been release especially if she is in activity. At the beginning of the year 2019 pus starts coming and made a bad smell (Fig. 1 A-B). Because of feeling uncomfortable of this condition, march 06th 2019 she sought out help to dermatology and venereology outpatient clinic of Dr. Soetomo General Hospital out dermatology and venereology. Patients hospitalized to treat secondary infections of her illness and wound treatment to reduce pus and bad smells

The physical examination of general state was all within normal limit. Blood pressure was 120/80 mmHg, pulse rate was 80 times per minute, respiratory rate was 20 times per minute. From head and neck, there were no signs of anemia, cyanosis, icterus, or dyspneu. From thorax examination, heart and lungs were normal. From abdomen, liver and spleen were not palpable. From her upper and lower extremities there were no edema and warm on palpation.

Dermatological examination on her right axillar region discovered multiple nodule eritematosa, with varying sizes, some vesicles and there were exudative clear fluid and pus (Fig. 1 A-C). The laboratory examination on March 06th 2019 was revealed: haemoglobin was 14,0 g/dL, white blood count 11.090/mm$^3$, thrombocyte 302.000/L, and hematocrite 41,2%. Microscopic findings from gram staining examination result leukosit 4-6, epitel 1-2, coccus gram positive 2. Blood culture examination result Pseudomonas aeruginosa, we gave oral therapy with clindamycin to reduce secondary infection.
Histological examination of the vesicle was revealed hyperkeratosis and acanthosis in the epidermis layer. Several lumen which is covered by a layer of endothelial cells containing eosinophilic amorphous material. Stroma is fibrous connective tissue with infiltration of neutrophil, lymphocyte, histocyte, and plasma cell inflammation in the dermis layer. There are no signs of malignancy and the conclusion according to lymphangioma sirkumskripta (Fig. 1 C-D).

Dermoscopy showed yellow lacunae surround by pale septa without inclusion of blood, and yellow to pink lacune dark-red or bluish lacunae. The picture of dermoscopy can be clearly seen on the Figure 4 below. The conclusion dermoscopy described as CLC. Fine needle aspiration biopsy showed Hypocellular smear contains the spread of mononuclear inflammatory cells and macrophages. Eosinophilic background. Conclusion benign lesion suggests a lymphavascular lesions (Fig. 1 E-H).

Based on these findings, from physical examination, histophatology and dermoscopy. The diagnosis of cutaneous lymphangioma circumscriptum was established. Treatments for this patient treated with cryotherapy (Fig. 2 A-C). After 6 treatments with cryotherapy every 2 weeks we observed no development of new lesions, vesicles and nodules are reduced (Fig. 3 A-C).
Figure 1. a,b) Location of the tumor c,d) histopathological examination e,f) dermaoscopy findings g,h) Fine Needle aspiration Biopsy findings

Figure 2. a) Cryotherapy 1st treatment b) Cryotherapy 2nd treatment. c) Cryotherapy 3rd treatment – multiple vesicles decrease, hard nodule getting smaller
Figure 3. a) Cryotherapy 4th treatment b) Cryotherapy 5th treatment – multiple vesicles decrease, hard nodule getting smaller, no progression new vesicles c) Cryotherapy 6th treatment – large nodules are reduced

Discussion

Lymphangiomas are congenital malformations, hamartomatous of the lymphatic system that may involve the skin and subcutaneous tissues. They can occur on any cutaneous surface or mucous membrane. The most common skin sites are the head and neck, proximal extremities, buttocks, and trunk, while the intestines, pancreas, and mesentery are other potentially affected organs. Their skin involvement ranges from small and well demarcated malformations to large, diffuse ones with unclear borders.6-8

Diagnosis of this case based on clinical features, dermoscopy and histopathology examination. From clinical features cutaneous lymphangioma, is characterized by persistent, multiple cluster of translucent vesicles that usually contain lymph fluid.

Dermoscopy findings red and pale homogenous area resembling vascular lagoons and whitish and yellowish areas with thin linear vessels. Histophatolo gy findings acanthosis, hyperkeratosis, and multiple dilated lymph vessels.

In 1877, Wegener classified lymphangiomas into three major groups: simple, cavernous, and cystic. Cutaneous lymphangioma circumscription (CLC), part of the simple group, was described by Fox and Fox in 1878. They named it “lymphangiectodes” It was renamed in 1889 to “lymphangioma circumscription” by Morris. Currently, however, lymphangiomas are divided into two major groups, superficial and deep, based on the
depth and size of the abnormal lymph vessels. The superficial group includes CLC, whereas the deeper group includes cavernous lymphangiomas and cystic hygromas. The lymphangiomas of the deeper group were once considered independent entities, but currently cystic hygroma is believed to be an aneurysmic variant of cavernous lymphangioma. It is possible for both groups to appear in the same patient. CLC is the common form of cutaneous lymphangiomas, one that may recur if improperly excised.7–10 Lymphangiomas are uncommon, accounting for 4% of all vascular tumors and about 25% of all benign vascular tumors in children. The incidence rate of lymphatic malformations is 1.2–2.8 per 1000 live births in the United States. About 50% of these are apparent at birth; 90% appear by appear by 2 years of age.

This is related to my patient she complaint since she was 10 months old. Gender differences have not been noted, except in a few reports in which females predominated males. Lymphangiomas may appear spontaneously in adolescence or adult life. No correlation among CLC, mucous membrane lymphangioma, or internal organ lymphangioma was found in a study by Flanagan et al. No familial histories of lymphangioma were noted either. Robust epidemiological evaluation may prove valuable.10–12

The pathogenesis of CLC was described in 1976 by Whimster et al. During development, abnormal lymphatic cisterns grow separately from normal lymph vessels in the deep subcutaneous tissue. These reservoirs may be a by product of a primitive lymphatic sac that has improperly connected with the rest of the lymphatic system. The cisterns have channels that allow them to communicate with ectopic lymph vessels. Contractions of the smooth muscle lining these cisterns will cause the abnormal ectopic lymph vessels to dilate and protrude from the skin.11–13

Regardless of the visible CLC size, the deep cisterns feed the surface lymphangioma. This is analogous to an ice-berg, where more lymphatic involvement is below the surface of the skin. Whimster’s observations are supported by those of lymphangiographic and radiographic studies. They reveal that large multilobulated cisterns extend deep in the
dermis and laterally beyond the obvious clinical view. The deep cisterns show no evidence of communication with the adjacent normal lymphatics. The absence of skin lymphedema further supports the presence of normal functioning lymphatics. The reason these primitive lymph sacs do not connect to the rest of the lymphatic system is unknown.\textsuperscript{14,15}

Cutaneous lymphangioma circumscriptum is typically seen as a small number of translucent cutaneous vesicles at or soon after birth, although possible at any age. They may range in size from minute vesicles to larger bullae. Specifically, 2–4 mm clusters of vesicles with pink, red, or black discoloration as a byproduct of hemorrhage are common. These vesicles often resemble frog spawn and tend to increase in number and size with occasional rupture leading to bleeding or drainage. Underlying lymphatic vessels occupy the dermal papilla and push upward against the epidermis, leading to a saccular appearance of the vesicles. CLC can also be found with hyperkeratosis and or verrucous changes, mimicking a warty appearance (Fig. 4 A-B).

The sites of predilection are the proximal extremities, trunk, axilla, and oral cavity, especially the tongue, but CLC may also occur on the penis, vulva, and scrotum.\textsuperscript{14–17} This is related to my patient she complaint multiple nodul eritematosa, with varying sizes, some vesicles.

\textbf{Figure 4.} a) Vesicles ranging from flesh colored to dark red and black as a result of blood leakage into the vesicles. b) verrucous appearing lymphangioma circumscriptum covering an area of 10 x 30 cm
Cutaneous lymphangioma circumscriptum was divided into two main groups, classic and localized, by Peachey and Lever in the 1970s. Although their clinical appearance is similar, the size, distribution, histology, and associated symptoms differ greatly between the two groups. According to Peachey et al., the classic form presents at or soon after birth and is often larger than a square centimeter. Sometimes a diffuse and palpable subcutaneous swelling is detectable before the appearance of vesicles. In classic CLC, it is uncommon for areas originally vesicular to become thick and develop warty plaques. Classic CLC usually occurs over the proximal part of the limbs, especially involving the upper arm, axilla, adjacent chest, and scapular regions. Localized swelling is often detectable in areas adjacent to the vesicles. The localized form, however, is seen at any age, is often <1 cm², and can appear anywhere on the body. In Peachey’s original study, 25% of patients were older than 45 years of age when presenting with the local form of CLC. Localized CLC usually does not present in the same regions as classic CLC. Cases with overlap of the two forms exist. In both forms, there is no evidence of the abnormal deep lymphatics communicating with the normal lymphatics.¹⁸

Dermatoscopic examination of CLC shows a lacunar/saccular pattern. Presence of clear fluid appears as light brown lacunas with pale septa. If blood has infiltrated in a patchy manner, scattered areas of redness appear within the lacunas. However, if there is homogeneous distribution of blood in the CLC, a pink hue overwhelms the lacunar structures (Figure 9 A-B). With marked blood presence in the CLC, dermatoscopic findings are indistinguishable from those of hemangiomas (Table 2).¹⁹

Lymphedema of the lower limb is also associated. CLC was identified in patients with concurrent cystic hygroma, possibly suggesting a generalized developmental disorder of the lymphatic system. Other common complications include cellulitis and bleeding. Involvement of unusual locations, such as the scrotum and viscera, may occur. Associations between lymphangioma and other conditions such as the Proteus, Cobb, and Maffucci syndromes were reported.²⁰
Malignant transformation of CLC is rare. A minute number of lymphangiosarcomas were noted on sites of CLC with prior radiation therapy. A Dabska tumor, or papillary intralymphatic angioendothelioma, was reported forming within an adolescent patient’s CLC. The lymphangioma recurred after excision, but the Dabska tumor did not. Squamous cell carcinoma has been described arising within CLC.²¹

**Table 2.** Dermatoscopic features of cutaneous lymphangioma circumscriptum (CLC)

| Dermatoscopic appearance | Underlying pathology |
|--------------------------|----------------------|
| Lacunar/saccular pattern of light brown lacunae with pale septa | CLC with clear fluid |
| Redness within lacunae | Minimal blood extravasation in CLC |
| Diffuse pink hue with pale septa | Modest blood contamination in CLC |
| Marked redness resembling hemangioma | Significant blood contamination in CLC |

**Figure 5.**

a) Dermoscopy - Red and pale homogenous areas resembling vascular lagoons. In some, a raised surface appeared due to the sedimentation of blood according to their corpuscles density, leading to a color transition from dark to light in some lacunae – Hypopyon-like (circles).

b) Dermoscopy – Whitish and yellowish lacunar areas with thin linear vessels

The vesicles of CLC represent an overpopulation of dilated lymphatic channels expanding within the papillary dermis. They can be associated with overlying
hyperkeratosis and acanthosis and may possess capillary tufts. These lymphatic channels are numerous in the papillary dermis and often extend below to the reticular dermis or subcutaneous tissue. The deepest vessels with which the CLC vesicles communicate tend to have a larger caliber and a thick wall composed of smooth muscle (Fig. 6 A-B).21,22

![Figure 6. a) Histological features showing grouped cystic lymphatic spaces present throughout the thickness of the dermis and lined with a flattened endothelium. (Hematoxylin & eosin x100) b) Cystic lymphatic space lined with a flattened endothelium in the dermis (Hematoxylin & eosin x400)](image)

Upper dermal vessels have a wide lumen, whereas deep dermal vessels have a narrow one. The lumen of all involved vessels is filled with lymphatic fluid and often red and white blood cells. The mechanism of red blood cell extravasation into the dilated lymphatics is unknown, but microshunts between capillaries and smaller lymphatics may be one source. The communicating channels are lined by flat endothelial cells which stain positive for Ulex europaeus agglutinin-1, a well known plant derived marker of endothelial cells. Markers including lymphatic vessel endothelial receptor 1 and vascular endothelial growth factor C are helpful in distinguishing lymphatic endothelial cells from those of blood vessels. The dermis often has numerous lymphocytes and shows evidence of fibroplasia.23

This patient from histological examination also was revealed hyperkeratosis, acanthosis, vesicles containing of red cells in its fluid. Result from dermoscopy examination revealed whitish and yellowish lacunar with thin vessel also there are
res and pale homogenous areas resembling vascular lagoon.

Ultrastructural analysis of lymphatic vessels of the upper and deep dermis demonstrates important differences. Endothelial cells of the upper dermal lymphatic vessels show higher electron density, are flattened (0.1–1.3 \( \mu \)m), and possess a well developed and partially multilayered basal lamina. The nuclei of the cells are oval or occasionally indented with peripherally condensed chromatin. The endothelial cells of the deep dermal lymphatic vessels are less flat (0.6–2.5 \( \mu \)m) and are separated from connective tissue by discontinuous basal lamina. The nucleus is slightly flattened with normal appearing chromatin. The cells of the deep dermal lymphatic vessels also have pinocytotic vesicles, formed from cell membrane invagination, which are not found in the cells of the upper dermal lymphatic vessels.\(^{24}\)

The differential diagnoses of CLC include the diseases listed in Table 3. Lymphangiectasis and metastatic carcinoma of the skin are notable Cutaneous metastasis of internal malignancy is particularly worrisome, as it may be a presenting sign of cancer. This entity often arises as a non-specific painless dermal or subcutaneous stony nodule with an intact epidermis that is flesh-colored, pink, violaceous, or brown–black. Violaceous papulovesicles that resembled CLC may be noted in telangiectatic metastatic breast carcinoma. Cutaneous metastasis occurs in 0.7–9.0% of all patients with cancer. CLC may resemble lymphangiectasis, a condition induced by lymphatic obstruction. In lymphangiectasis, previous surgery or radiation therapy has often been performed in the affected area, resulting in identical histology as CLC but a different pathogenesis. Smaller CLC can resemble warts, molluscum contagiosum, hemangioma, angiokeratoma, or lymphangioendothelioma.\(^{24,25}\)
Table 3. Characteristics of cutaneous lymphangioma circumscriptum and selected differential diagnoses

| Diagnosis                                | Appearance                                                                 | Distribution                                                                 |
|------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Cutaneous lymphangioma circumscriptum    | Scattered or grouped vesicles ranging from minute to >5 mm overlying normal skin or papules. Plaque-like or warty hyperkeratosis possible. Colors range from clear, pink, red, purple, or black | Proximal part of limbs (classic form) or all cutaneous surfaces (localized form) |
| Lymphangiectasis                         | Fluid-filled vesicles ranging from clear to smooth, flesh-colored nodules   | All cutaneous surfaces, often appearing along an incisional scar               |
| Cutaneous metastasis (carcinoma telangiectodes) | Nodules – often nonpainful, round or oval, firm, mobile, and rubbery. Flesh colored to brown, blue-black, or red and purple. Sizes ranging from minute to large tumors | Often near the site of primary tumor                                           |
| Hemangioma                               | Hypopigmented macule ranging to a bruise-like, red, or blue macule. Strawberry like or nodular violaceous forms possible | Head and neck most common, followed by trunk, lower extremities, and upper extremities |

There is no pharmacologic treatment for CLC. The main considerations are cosmetic outcome, continued lymphatic and blood leakage, pain, swelling, and persistent superinfections. Antibiotics are used for secondary infections, primarily Staphylococcus aureus. Surgical excision is the approach of choice for primary treatment of lymphangiomas. The objective is to remove as much of the lymphangioma as possible so as to avoid recurrence. Excision should be through the full thickness of skin and subcutaneous tissue and down to the deep fascia until normal subcutaneous tissue is exposed. This eliminates the abnormal hypertrophied lymphatic cisterns which serve as sites of recurrence. Frozen section analysis of the lateral and deep sections ensures clear margins. If confined to the superficial dermis, the malformation is more amenable to surgery and possesses longer lasting results.\textsuperscript{25} In this case treated with cefadroxil to treat secondary infections and cryotherapy. After 6 treatments with cryotherapy every 2 weeks we observed no development of new lesions, reduced vesicles and nodules.

Cryotherapy has been reported 75% good outcomes to reduction in the size of an CLC lesion after 5 session of Cryotherapy 2 week intervals.\textsuperscript{25} In this case after 6 treatments with cryotherapy every 2 weeks we observed no development of new lesions, reduced vesicles and nodules. In this case patient still need cryotherapy treatment 2 week intervals until there is no more lesion.
Radiation therapy should be avoided, as malignant conversion is possible. Sclerotherapy with hypertonic saline may be successfully employed. In multiple cysts the technique was only useful as a presurgical adjunct.\textsuperscript{25} This patient also show good result treated with cryotherapy after 6 times treatment vesicle and nodule are reduces and there no comes fluid from the lesion.

**Conclusion**

In summary, we can conclude that cutaneous lymphangioma circumscriptum (CLC) is a rare congenital malformation of superficial cutaneous lymphatic duct. The clinical dermatoscopy and histopathological correlation is great importance. The objective is to remove as much of the lymphangioma as possible so as to avoid recurrence. Cryotherapy, have been utilized with good outcomes. Cutaneous lymphangioma circumscriptum is an evolving situation with ongoing discoveries and further research needs.

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