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Burn Hemangioma (BH) (Scalded Pyogenic Granuloma) versus Infantile Hemangioma: Report of Six Cases of BH and Its Effective Therapy with Oral Propranolol

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Abstract

Infantile hemangioma and burn hemangioma have many similarities in clinical pictures, pathology and treatment. As infantile hemangioma appears usually after birth and then rapidly grow within few months and then a statue state and then involutes within few years while burn hemangioma so called burn pyogenic granuloma usually appears within days after burn with liquid and grow rapidly into many giant angiomatous masses and then after short time usually weeks or months will involute in more than 37.5% of cases. Hence burn hemangioma and infantile hemangioma sharing many similar features as both are angiomatous with dramatic rapid proliferation of blood vessels that followed by involution but with different time periods and both carry CD133 and CD34 for infantile hemangioma and CD34 for burn hemangioma. Also infantile hemangioma rapidly responds to systemic propranolol and similarly do in cases of burn hemangioma. Accordingly it is more better scientifically to call scalded pyogenic granuloma burn hemangioma. The objective of the present report is to review these conditions and do comparison between them and also to record 6 cases of burn hemangioma and its effective therapy with oral propranolol.

Keywords

Burn Hemangioma, Infantile Hemangioma, Oral Propranolol

1. Introduction

1.1. Infantile Haemangiomas

Infantile hemangioma (IH) are benign vascular tumors that appear during the first months of life characterized by a pattern of rapid proliferation, followed by a slower period of involution [1] and are the most common pediatric tumors, affecting 10% - 12% of infants by the first year of life [2] [3]. They are more commonly observed in girls than boys with preponderance between 3 and 5:1 [4] [5]. Also it is apparent that haemangiomas are more common in premature infants, appearing in up to 30% of babies less than 1000 g and 15% of babies less than 1500 g [3] [6] [7]. The lesions are soft and easily compressed with sharp borders. In general, they tend to grow over the first year or so, remain stable for a period of months, and then slowly involute spontaneously (**Figure 1**). The period of greatest growth is the first 5 months. Ulceration as a complication might occur in nearly 16% of lesions, usually by 4 months of age especially in the genital area [8].

Around 30% of cases resolve by the third year, 50% by age 5, and 70% by the time the patient is 7 years of age. The skin may appear normal after involution, but more commonly, atrophy, telangiectasia, or anetoderma-type redundancy is observed [8].

1.2. Pathogenesis

The pathogenesis of infantile hemangiomas is complex and several hypotheses have been suggested:

1) CD133+ stem cells within the hemangioma differentiate into mature blood vessels that express GLUT-1 (a glucose transporter normally restricted to endothelial cells with blood-tissue barrier function, such as in brain and placenta). The vessels proliferate, and then involute. It has been suggested that the stem cells could originate from placental trophoblast [8].

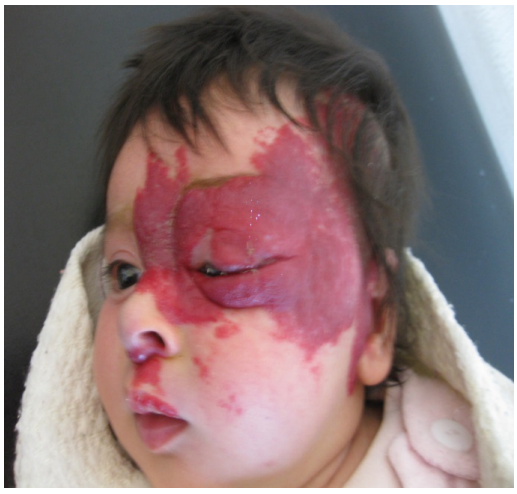


Figure 1. Showing infantile hemangioma. (Courtesy of *Prof. Sharquie*).

2) Several signaling pathways have been linked with IH pathogenesis, with the vascular endothelial growth factor-A (VEGF-A) pathway being the key one. VEGF-A is a master regulator of angiogenesis and vasculogenesis. It is present at higher levels in the proliferating phase as compared with the involution phase of IH. Also its level in the serum of patients with IH is decreased following systemic steroid therapy. The high expression of VEGF could be related to hypoxia, as increased hypoxia inducible factor (HIF)-1a stabilization was recorded in patients with proliferating IH. The corticosteroids dramatically down regulate VEGF-A secretion by HemSCVEGF-A binding to three tyrosine kinase receptors, VEGFR-1, VEGFR-2 and VEGFR-3 and VEGFR-2 appears to mediate almost all the known angiogenic responses to VEGF-A [9].

1.3. Histopathology

During the period of growth in early infancy, capillary hemangiomas show considerable proliferation of their endothelial cells. The endothelial cells are large, mitotically active, and aggregated predominantly in solid strands and masses in which there are only a few small capillary lumina. Not uncommonly crystalline intracytoplasmic inclusions can be seen in the endothelial cells. In maturing lesions, the capillary lumina are wider and the lining endothelial cells then appear flatter but in the involution phase, there is progressive fibrosis with disappearance of the blood vessels 9 (**Figure 2**). Ultra-structural and immunohistochemical studies of capillary hemangiomas have shown that tumors demonstrate remarkable cellular heterogeneity. A large proportion of the cells in a given tumor are endothelial cells and pericytes, but fibroblasts and mast cells could also be seen. A complex interaction among these cell populations may modulate the progression and latter evolution of capillary hemangioma [10].

1.4. Markers of Infantile Hemangiomas

Infantile hemangiomas stain positive for Isoform 1 of the human glucose transport

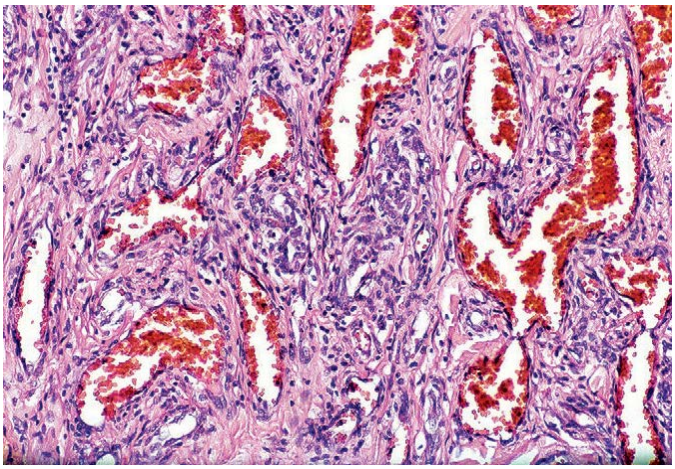


Figure 2. Histopathology of infantile hemangioma. (Courtesy, *Ronald P Rapini*) [11].

protein (GLUT1) highly sensitive and specific marker for identification of HIs in any organ. But GLUT1 is not expressed in the cells of various vascular malformation, pyogenic granuloma and hemangioendothelioma [12]. In addition, young early hemangiomas show evidence of endothelial progenitor cells that stain positive with CD133 and CD34 [8] and CD31 [12].

1.5. Treatment

Infantile hemangiomas usually involutes spontaneously after years but should be treated especially when lesions near or adjacent vital organ like face, eyes, nose and genital areas. Also hemangiomas must be treated to avoid complications and to minimize psychological stress [8].

There are many modalities of treatment available including topical and systemic therapies:

1.6. Topical

- Intralesional corticosteroids [13].
- Topical steroids. Potent steroids have been used to treat flat or minimally raised vascular plaques of IH particularly at sites prone to ulcerations and disfigurement [14].
- Topical imiquimod with its ability to induce the production of interferon, tumor necrosis factor-alpha, and the anti-angiogenesis factor tissue inhibitor of matrix metalloproteinase may be most effective in superficial IH [15].
- Topical β-blockers are now used for lesions with both deep and superficial components and those that are amblyogenic. When initiated in the proliferative phase of the lesion, the effectiveness of the treatment can be seen within days [16].

1.7. Systemic

- Systemic corticosteroids. Corticosteroids have been shown to suppress VEGF production by hemangioma-derived stem cells and to inhibit vasculogenesis in a murine model [13].
- Systemic β-blockers. Hemangioma endothelial cells express β2-adrenergic receptors, and effects of propranolol include vasoconstriction, decreased expression of pro-angiogenic factors (e.g. VEGF, bFGF), and induction of endothelial cell apoptosis [13].
- Other systemic therapies like vincristine and Recombinant interferon-α (2a and 2b) can also inhibit angiogenesis [13].
- Surgical and Laser Therapies [13] might be suggested in certain critical situations but these are rarely indicated at the time being.

1.8. Pyogenic Granuloma

Pyogenic granuloma (PG) are common acquired vascular tumors that most commonly appear on the skinbut may also affect mucosal surfaces and may

rarely be found in a subcutaneous or visceral location. They are most common seen in children, particularly in those younger than 5 years old. They are commonly seen on the head and neck. Removal of these benign tumors is often sought because of their appearance and tendency to bleed. Many therapeutic modalities are used including cryotherapy, excision with primary closure, curettage, shave removal, electro-cautery, injection of sclerosingagents, and a variety of laser modalities. These options may cause scarring and may provoke pain and anxiety in children. Nonsurgical options, including the use of topical imiquimod or silver nitrate, provide a variable response and may be complicated by dermatitis. Some early pyogenic granulomas may regress spontaneously. The recurrence rate after treatment varies and can be as high as 15%, with surgical management having the best response and lowest recurrence risk [17] [18]. Noninvasive therapies are being sought, particularly in children, because of high recurrence rates, procedure-associated anxiety, and complications such as scarring as cutaneous and mucosal pyogenic granulomas have been treated successfully using oral or topical β-blockers [19].

Although the pathogenesis of pyogenic granuloma is not completely understood, it has been hypothesized that local tissue hypoxia or trauma induces these tumors and that they result from aberrant healing. The expression pattern of angiogenic factors supports this hypothesis [20]. In particular, endothelial cells undergoing cellular stress express VEGF and bFGF [21]. Local inflammatory cells within pyogenic granulomas may also contribute to VEGF expression [22] (**Figure 3**).

1.9. Histopathology

The essential lesion is a well-circumscribed, exophytic, sometimes pedunculated,

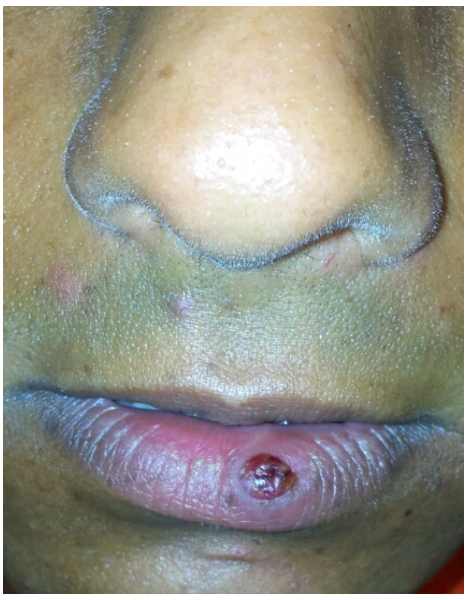


Figure 3. Showing pyogenic granuloma on the lower lip. (Courtesy of *Prof. Sharquie*).

proliferation of small capillaries, often arranged in a lobular pattern. Lesional capillaries are lined by flattened to slightly plump endothelial cells, rimmed by pericytes, and surrounded by a variably edematous fibro-myxoid interstitial stroma containing fibroblasts. Endothelial and stromal cell mitotic activity is highly variable and depends on the stage of growth; a scant infiltrate of lymphocytes, plasma cells and mast cells may be present [23]. The angiomatous tissue is composed of a variably dilated network of blood-filled capillary vessels and groups of poorly canalized vascular tufts [24]. Alsothick intervening bands of dense fibrous tissue sharply define the lobularityand help distinguish pyogenic granuloma from other lobular forms of capillary proliferation such as infantile hemangioma (**Figure 4**) [23].

1.10. Markers of PG

Immunohistochemicalstains for endothelial markers like CD34, CD31, factor VIII-related antigen, and Ulexeuropaeus are positive [25].

1.11. Burn Hemangioma (Scalded Pyogenic Granuloma)

Burn hemangioma (BH) is a commonvariant of pyogenic granuloma that presents dramatic clinical features which are different from those with classic pyogenic granuloma. Most patients are infants and young children and all patients had history of second degree burns with liquids like milk initially. BH acutely erupted between 1 and 4 weeks in patients' burned area, which may be infected by bacteria, fungus and virus. And, can be classified into proliferative growth and shriveling involution stages and static period in between [26]. Burn hemangiomaare usually multiple and eruptive [27]. That appear after around 2 weeks or so after burn with hot milk and then multiply rapidly to form multiple angiomatous masses that tend to coalesce together to form huge lobulated red gray masses and these remain for months, then involute spontaneously in about 37.5% of cases without interventions simulating phases of infantile hemangioma [26] [28].

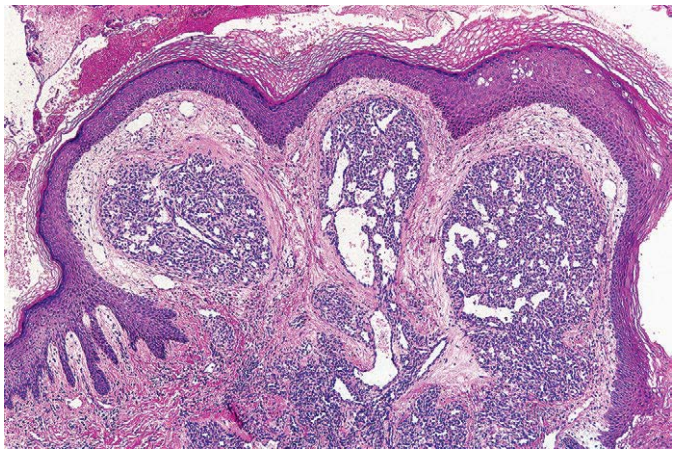


Figure 4. Histopathology of pyogenic granuloma. (Courtesy, *Ronald P Rapini*) [11].

1.12. Pathology and Markers

The pathology showed three histological characteristics including hyperkeratosis, or acanthosis of epidermis, numerous newly proliferative vascular edematous stroma with infiltration by plasma cell and lymphocytes [26]. Marker for DC34 is positive (**Figure 5**) [29].

1.13. Treatment

Conservative treatment including wound management and antibiotic could be chosen firstly, especially when large PGBs are on the face or other important area of one's body. When conservative treatment is ineffective, a surgery could be chosen including cautery, cryo-therapy, and surgical excision with primary closure or with grafting [26].

2. Case Report

2.1. First Case

Nine months-old male with multiple hemangiomas on his abdomen after a second degree burn with hot tea. The lesions appeared around 10 days after burn and these lesions were increased in number and size to form big giant masses within two weeks. The patient was treated with supportive therapy using systemic and topical antibiotic including oral amoxicillin and fucidine ointment but there was little improvement with appearance of new lesions and getting larger in size. On examination, there were multiple giant mass with large nodules on the abdomen. These lesions were red grey non-tender soft on palpation seen on healed 2nd burn (**Figure 6**). The patient was treated again with conservative therapy but lost follow up.

2.2. Second Case

A 10 months old male presented with burn hemangiomas on the left foot after a

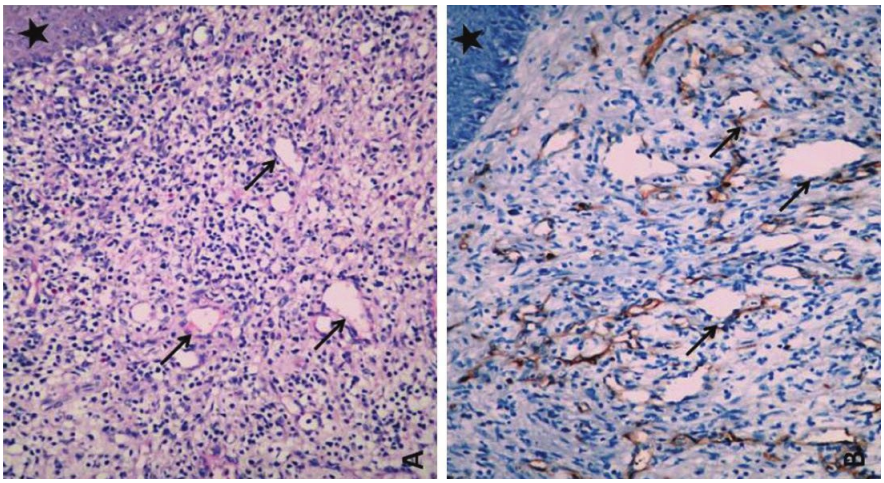


Figure 5. Showing histopathology and CD34 marker of scalded burn pyogenic granuloma (burn hemangioma) [29].

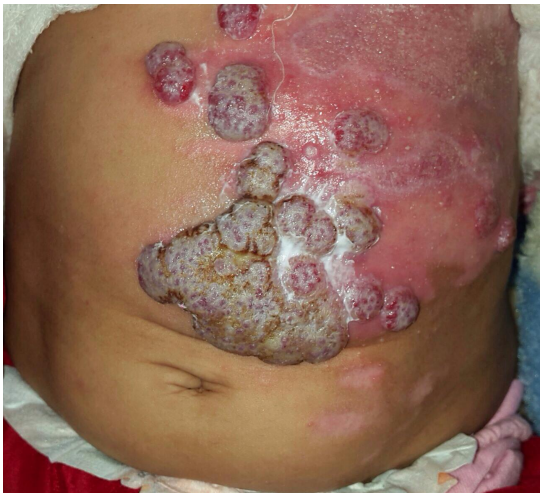


Figure 6. The appearance of multiple disseminated burn hemangioma on the abdomen after 10 days following second degree burn with hot tea.

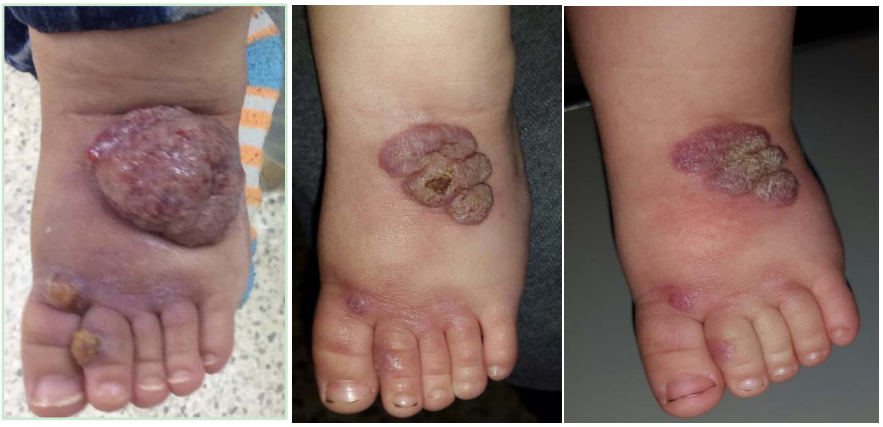
second degree burn with a hot tea. The lesions appeared after 12 days of burn and were small lesions but rapidly enlarged in size and number and matted together to form large non-itchy lesions with occasional bleeding on trauma. On examination, there were three masses red gray in color non-tender and does not bleed easily. There were one giant mass and two small nodules. The patient was managed with topical and systemic antibiotics with no benefit and surgical excision was suggested but was refused. We introduced oral propranolol at a dose of 5 mg twice daily and after two weeks there was marked improvement, then the dose increased to 10 mg at morning and 5 mg at night and after another 2 weeks there was much better improvement (**Figure 7(a)-(c)**).

2.3. Third Case

Twenty five years old female with acne scar and thermaldermabration was done for her scarring. She presented after two weeks with big angiomatous lesions on the right cheek. On examination, there was one big red grey non-tender soft mass on the right cheek. The lesion was resolved by using supportive therapy like topical and systemic ointment within 2 weeks.

2.4. Fourth Case

Three years old male patient presented with history of burn with boiling tea of one month duration that followed by appearance of angiomatous nodules and masses on the left lower limb that developed 2 weeks following burn. Onexamination, there were multiple angiomatous compressible non-tender nodules and masses red grayish in color that were located on different areas of left thigh with non-healing deep burn on the inner side of left thigh. This rash only seen on healed 2nd burn hypopigmented skin while avoiding deep non-healed ulcerated burnt skin (**Figures 8(a)-(c)**). The burn was treated conservatively using topical



(a) (b) (c)

Figure 7. (a) Showing giant mass and two large nodules of burn hemangiomaon healed 2nd degree of left foot. (b) The appearances of lesions 2 weeks after treatment with propranolol 5 mg twice daily. (c) The appearance of lesions one month after the first visit after increasing the dose of propranolol to 10 mg at morning and 5 mg at night.

and systemic antibiotics but surprisingly there was marked exacerbation and increase in size of all masses of hemangioma. (**Figure 8(d)**). Small lesion was excised for biopsy and processed and stained with Hematoxylin and Eosin stain (H&E stain), the result was as follow:

There was marked pseudoepitheliomatous hyperplasia in some sites while there was thinning and atrophy in other sites of the epidermis; otherwise there were no pathological changes. While in the dermis there was severe edema and marked proliferation of blood vessels, some of them were very small while the others were big dilated, these blood vessels were lined by prominent endothelial cell in some areas while in other sites were small blood vessels and still not well lined by endothelial cells. The infiltration was composed mainly of eosinophils, lymphocytes and histiocytes and in some areas neutrophils. These infiltrates were mainly extra-vascular but some of them intravascular (**Figures 9(a)-(c)**).

Oral propranolol 10 mg three times a day was started together with antibiotic for 2 weeks. There was marked improvement that started few days after therapy and was most obvious after two weeks (**Figure 8(e)**). After another two weeks of propranolol therapy, there was more marked response (**Figure 8(f)**). Also there was marked healing of the deep burn on the inner side of the right thigh following propranolol therapy (**Figure 8(g)**).

2.5. Fifth Case

Seven years old female with history of burn of lower limbs is with hot tea of 6 weeks duration. The burn was treated with topical and systemic antibiotic but rash appeared examination; there were numerous nodules and masses on top of burn of both lower limbs and natal cleft. The masses were red grayish angiomatous compressible non-tender lesions that were seen only on healed 2nd degree burn while avoiding the deep non-healed burn, (**Figures 10(a)**, **Figures 10(b)**). The patient was managed conservatively but he was lost follow up.

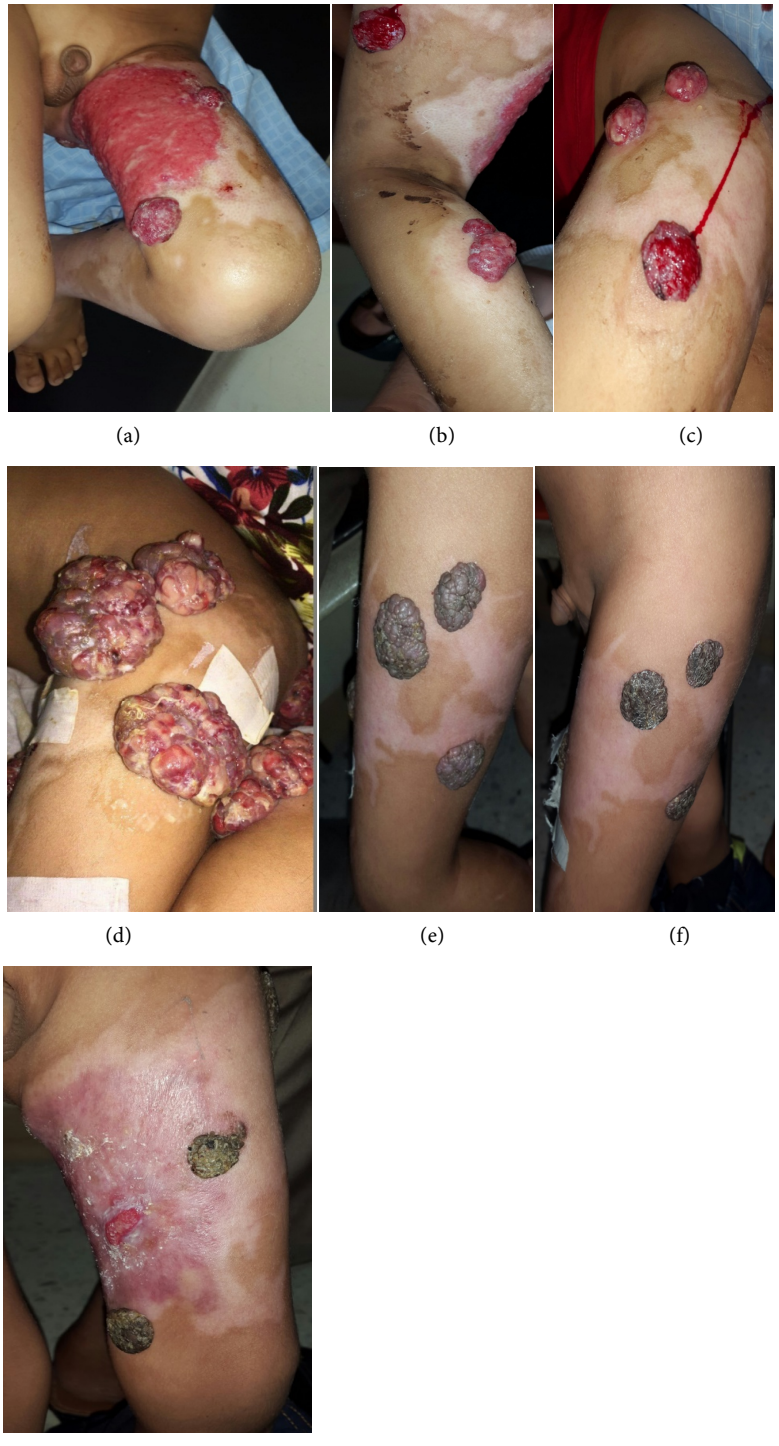
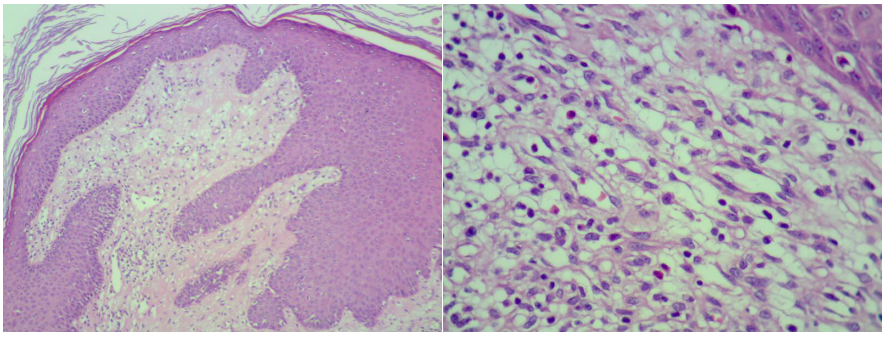
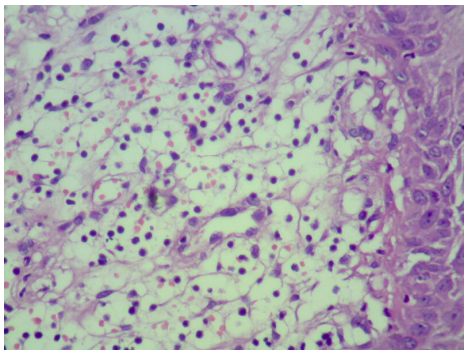


Figure 8. (a)-(c) Showing 3 years old male patient with burn hemangioma on healed 2nd degree burn while skipping deep non-healed burn area. (d) The same patient 7 days after antibiotic cover showing marked increase in size of burn hemangioma. (e) The same patient showing marked reduction and improvement of burn hemangioma following 2 weeks therapy with propranolol. (f) Showing more reduction of hemangioma mass after 4 weeks of propranolol therapy. (g) Showing marked healing of the deep burn 4 weeks after oral propranolol therapy.

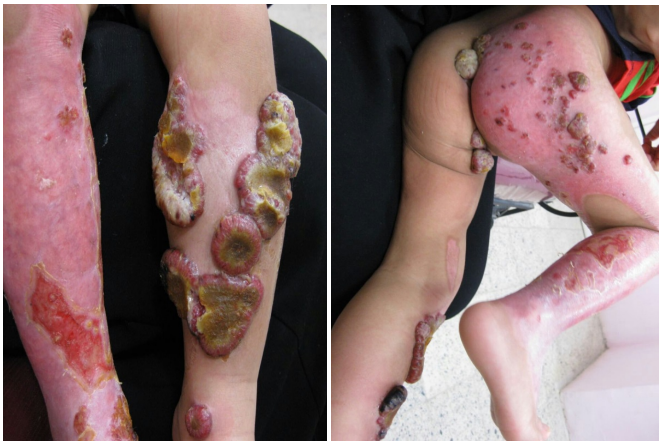


(a) (b)



(c)

Figure 9. (a) Showing histopathology of burn hemangioma, mainly pseudoepitheliomotus hyperplasia with new vascularization and dermal infiltrate. Original magnification ×40. (b) Showing numerous blood vessels with dermal infiltrates consisting mainly eosinophil and lymphocytes. Original magnification ×400. (c) Showing new vascularization with dermal infiltrate. Original magnification ×400.



(a) (b)

Figure 10. (a)-(b) Seven year old female patient showing burn hemangioma on healed 2nd burn while escaping the non-healed deep ulcerative burn.

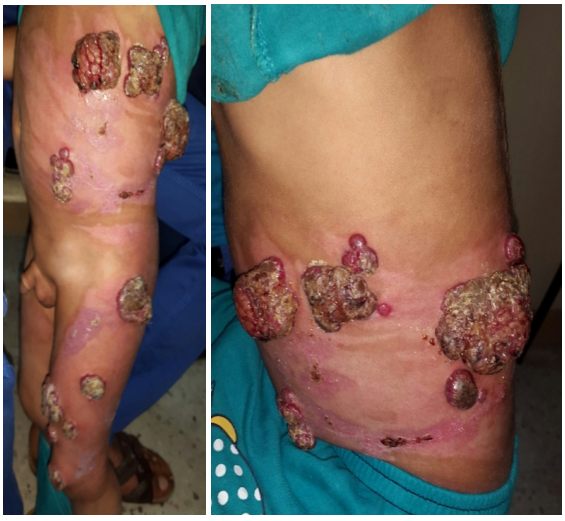
2.6. Sixth Case

Boy aged 2.5 years presented with a non-itchy rash affecting the left side of abdomen and left lower limb of 17 days duration that appeared 10 days after a history of burn with boiling soup. These masses were gradually increasing in size

and number till time of presentation. Onexamination, there were small and big angiomatous masses and nodules affecting left side of abdomen and left thigh that were located on top of partially healed hypo-pigmented 2nd degree burn (**Figure 11(a)**, **Figure 11(b)**). This rash was non-tender red and reddish grayish in color. The burn was treated with conservative therapy including topical and systemic antibiotics but although there was healing of burn but new rash started to be seen 10 days after time of burn. Oral propranolol 10 mg twice a day was given together with topical potassium permanganate solution to be seen after 10 days but patient lost follow up.

3. Discussion

Scalded pyogenic granuloma (Burn Hemangioma) which is a variant of hemangioma that presents with dramatic clinical features which are different from those with classic pyogenic granuloma [26]. The differences between burn hemangioma from classic pyogenic granuloma include: multiple and eruptive masses, huge and localized to the area of burn [26] [27]. The burn hemangioma passes into 3 phases of evolution within short period of time as there is proliferative growth phase that starts within 1 - 2 weeks after burn where angiomatous lesions will appear that enlarge quickly into large giant masses that might remain for months and then start to involutes. The histopathology is angiomatous with marker positivity for CD34 [26] [29]. In the present study we reported six cases with typical picture of burn hemangioma that followed burn with hot tea, soupand thermal dermabrasion and this is in contrast with other reports where burn with milk was the common history although burn hemangioma had followed lightening. Also the present report of 6 cases of hemangioma had shown typical phases of evolution like growth proliferative phase, static phase and



(a) (b)

Figure 11. (a)-(b) Showing burn hemangioma consisting of red and greyish red angiomatous masses located on healed 2nd degree burn.

involution phase.

To my surprise, I had seen the present five cases within winter of 2015-2016 but only one case during 1986. So definitely there is upsurge of these cases of burn hemangioma but what is the reason behind this increase? It is difficult to be answered at the time being.

The pathogenesis of BH: in many cases, including cases in the present study, have shown the burn hemangioma only develop after superficial burn especially 2nd degree burn and avoiding areas where there is deep burn causing severe damage to all elements of dermis that followed by fibrosis and keloid formation. Hence we can hypothesize that BH develop only when there is mild or partial damage to constituents of dermis and this will provoke endothelial-haematopoietic stem/progenitor marker CD34 to divide and proliferate, followed by release VEGF-A that will initiate angiogenesis and vasculogenesis, thus forming angiomatous reaction and followed by BH [30].

The clinical picture and evolution of burn hemangioma is very comparable to infantile hemangioma [30], hence it is better to name scalded pyogenic granuloma burn hemangioma (Table 1) as both sharing similar pathology, both infantile hemangiomas and burn hemangiomas are angiomatous histologically, show considerable proliferation of their endothelial cells. The endothelial cells are large, mitotically active, tumors show remarkable cellular heterogeneity. A large proportion of the cells in a given tumor are endothelial cells and pericytes, but fibroblasts and mast cells are also present [10]. VEGF-A is a master regulator of angiogenesis and vasculogenesis. It has been hypothesized that this angiogenic factor lead to the evolution of these tumors [9]. CD34, CD133 and CD31 positive in IH and CD34 for BH [8] [12] [25] [29].

Also both have similar evolution phases but with different time peroids. Also both share similar specific markers like CD34 [8] [29]. Regarding therapy of BH, the present study showed for the first time, marked improvement of burn

Table 1. Showing sharing similarities between infantile hemangioma and burn hemangioma.

Infantile Hemangioma	Burn Hemangioma
A common variant of hemangioma.	Not uncommon variant of hemangioma.
Disease of infants.	Disease of infants and children rarely adults.
The course is rapid eruptive immediately after birth.	The course is also rapid eruptive but after 2nd degree burn.
Three phases of growth: proliferation, static and involutions but each phase within years.	Also three phases of growth but time within weeks and months.
Pathology is angiomatous with positive CD markers but mainly CD133 and CD34.	Also angiomatous with positive CD markers specifically CD34.
Spontaneous involution is highly positive but within years.	Spontaneous involution is also highly positive but within weeks and months.
Therapy is including surgery, laser and propranolol.	Therapy is also including surgery, laser and propranolol.

hemangioma following oral propranolol therapy and this was similar to therapy of infantile hemangioma and pyogenic granuloma by oral propranolol [14] [19].

The present study is the first one to use oral propranolol in treatment of BH and showed rapid early response with few days and followed by marked reduction of masses of BH. Also oral propranolol showed rapid marked healing of deep burn on the medial side of the thigh and this observation was similarly reported. [31]

Infantile Hemangioma treated with topical and systemic β-blockers. Where hemangioma endothelial cells express β2-adrenergic receptors, and effects of propranolol include vasoconstriction, decreased expression of pro-angiogenic factors (e.g. VEGF, bFGF), and induction of endothelial cell apoptosis [13].

Although spontaneous involution of burn hemangioma is common feature but because the course of this disease is dramatic similar to IH, presenting with large multiple giant angiomatous masses, hence treatment is mandatory. Conservative therapy using topical and systemic antibiotics could be useful regimen but surgical excision is rarely needed and only in critical cases. The use of oral propranolol is probably is going to be main hope for this disease as has been suggested by the present study.

4. Conclusion

Burn hemangioma has many sharing similarities with infantile hemangioma regarding clinical picture, histopathology and markers and therapy. Oral propranolol was an effective therapy for BH. Hence oral propranolol is strongly indicated in burn hemangioma rather than surgical excision. Further study in this field is highly recommended.

Disclosure

This study was an independent study and not funded by any drug companies.

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