ANALYSIS OF CLINICAL MANIFESTATIONS OF PORT WINE STAIN PATIENTS AT THE INSTITUTE OF DERMATOLOGY, THAILAND: A 5-YEAR RETROSPECTIVE STUDY

BY

KETTYA HONG

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE
IN DERMATOLOGY AND DERMATOSURGERY
(INTERNATIONAL PROGRAM)
COLLEGE OF MEDICINE

GRADUATE SCHOOL, RANGSIT UNIVERSITY
ACADEMIC YEAR 2024

Thesis entitled

ANALYSIS OF CLINICAL MANIFESTATIONS OF PORT WINE STAIN PATIENTS AT THE INSTITUTE OF DERMATOLOGY, THAILAND: A 5-YEAR RETROSPECTIVE STUDY

by

KETTYA HONG

was submitted in partial fulfillment of the requirements
for the degree of Master of Science in Dermatology and Dermatosurgery

Rangsit University
Academic Year 2024

Assoc.Prof.Dr. Direkrit Chiewchengchol, M.D., Ph.D.
Examination Committee Chairperson

Dr. Praneet Sajjachareonpong, M.D.
Member

Dr. Wanida Limpongsanurak, M.D.
Member and Advisor

Approved by Graduate School

(Prof. Suejit Pechprasarn, Ph.D.)
Dean of Graduate School
August 23, 2024

Acknowledgments

I would like to express my deepest gratitude and appreciation to everyone who have engaged to the accomplishment of this research study. Without their support and guidance, this research would not have been possible.

Primarily, I am immensely thankful to my supervisor, Sirinda Jamjanya, for her continuous support and priceless mentorship throughout this research project.

I am also grateful to the members of my research committee, teachers from Institute of Dermatology and Rangsit University, for their suggestions and insightful comments that have enhanced the quality of this project. Their expertise has been truly inspiring, and I am honored to have had the opportunity to get to learn every single step from them.

Furthermore, I would like to extend my appreciation to Bongsrey Pich Chanmony who have provided me with moral support and encouragement during challenging times.

Last but not least, I am deeply thankful to my dad Hay Hong, my mum Khis Kimly, my both sisters, Hong Vannida and Hong Kaknika, my grandparents, my friends and colleagues for their unwavering love and support throughout this journey.

To all those mentioned above and to anyone else who has contributed in any way to this study, I offer my heartfelt thanks. I am truly grateful for everything you have done.

Kettya Hong

Researcher

6406184 : Kettya Hong

Thesis Title : Analysis of Clinical Manifestations of Port Wine Stain Patients at the Institute of Dermatology, Thailand: A 5-Year Retrospective Study

Program : Master of Science in Dermatology and Dermatosurgery

Thesis Advisor : Dr. Wanida Limpongsanurak, M.D.

Abstract

Port wine stains (PWS) are progressive capillary vascular malformations. Various publications have reported different results concerning the natural history of PWS. The objective of this study was to analyze the clinical manifestations of PWS, encompassing the type of lesions, associated anomalies, and their interrelationships. Data were collected from PWS patients in the Institute of Dermatology, from 2018 to 2023. This retrospective study included 135 patients, with an average age of 27.11 years. The proportion of females (55.6%). The face was the most common location (58.5%), with the majority of lesions appearing red (63.7%) and predominantly flat (68.9%). However, hypertrophic and nodular lesions were present in 20% and 10.4% of cases, respectively. The different age groups between hypertrophic and nodular lesions of PWS were significant (P-value = 0.022). Hypertrophic PWS patients had the highest proportion in the age range of 11-20 years, whereas Nodule PWS patients had the highest proportion in the age range of 31-40 years. Purple lesions were significantly associated with hypertrophic PW. The V3, upper lip, lower lip, and oral mucosa exhibited a significant difference in hypertrophic PWS.

In conclusion, the findings of this study contribute to a better understanding of PWS's natural history, adding value to a more comprehensive approach to its management. However, advancing future research will be essential for obtaining more information.

(Total 68 pages)

Keywords: Port-wine Stains, Capillary Vascular Malformation, Hypertrophic lesion, Nodular lesion

Student's Signature ..... Thesis Advisor's Signature .....

Table of Contents

Table of Contents (continued)

Table of Contents (continued)

List of Tables

Page

Tables

List of Figures

Page

Figures

Chapter 1

Introduction

1.1 Background and Significance of the Problem

Port wine stains (PWS) are birthmarks caused by malformations of blood vessels in the skin. PWS affects 0.3-0.9% of newborns. Males and females are equal.(Han et al., 2020) It appears as a flat, pink, or red mark, thin macular lesions during infancy, and does not regress spontaneously. Without treatment, it might progressively become darker and thicker with a nodule or cobblestone appearance in adult life.(Faurschou, Olesen, Leonardi-Bee, & Haedersdal, 2011; Raath et al., 2020; Tark, Lew & Lee, 2011; Wanitphakdeedecha et al., 2021)

Lee et al. published a study to investigate the incidence and age of onset of PWS in 160 individuals. According to the study's findings, the beginning age of hypertrophy ranged from 1 year to 29 years. On average, soft tissue hypertrophy begins around the age of nine, and the most common site is the V2/maxillary segment, which is associated with upper lip enlargement. Bony hypertrophy begins at the age of 15 years, whereas nodule development begins around the age of 22 years.(Lee, Chung, Cerrati, & Waner, 2015) Klapman and Yao's study found that PWS thickness peaked in the twenties to 39-year age group, and was more common in men. They mentioned that thickening alone was most often red, thickening with nodules was most often purple, and nodules were associated with all 3 colors, least often pink.(Klapman & Yao, 2001) If left untreated, PWS progresses from a faint, pink macule to the more distinctive reddish-purple hue and develops soft tissue enlargement, bone hypertrophy, and/or nodule development of the affected tissues

(Klapman & Yao, 2001; Lee et al., 2015)

The most common location are the head and neck.(Brightman, Geronemus, & Reddy, 2015; Faurschou et al., 2011) This location of the lesions is really effective for cosmetical and psychological health. Although isolated PWS are generally thought to be asymptomatic, PWS can also cause functional impairment, skin and soft tissue hypertrophy, as well as ophthalmologic complications, particularly glaucoma.(Arisa, Ortiz, & Nelson, 2012; Raath et al., 2020)

There are many vascular selective lasers to treat PWS, but some are less effective and are not being used anymore. Among these laser treatments, the gold standard therapy for PWS is pulsed dye laser (PDL), which is the most commonly used and best studied. (Brightman et al., 2015; Tran, Kelly, Drolet, Krakowski, & Arkin, 2021; Raath et al., 2021) Although the earlier therapy begins, the greater the effectiveness, the articles on the treatment response rate differ. Wenhao et al. said that the response of PDL is related to the lesion size, anatomical region, kind of lesion, such as pink/red/violaceous or flat/hypertrophic, and a number of treatments.(Asahina et al., 2006) Some articles published about the poor prognosis related to treatment include treating the lesions located on the extremities; size larger than 80 cm2; receiving treatment after age 50; hyperplastic lesions are also less responsive to PDL; and infants with bilateral lesions.(Hsiao & Chang, 2011; Kelly et al., 2005; Ortiz & Nelson, 2012; Shi et al., 2014) Geographic stains have a poor prognosis for limb hypertrophy and related consequences.(Ortiz & Nelson, 2012) Lighter skin types are reported to be more responsive to treatment than darker skin types.(Asahina et al., 2006)

The literatures reviews on natural PWS courses are not well established at the moment. In this retrospective study, we will collect the clinical manifestations of any age. It is important to know how the lesions begin and what the consequences are if the patients

leave them untreated so that we can provide patients with more accurate information about the time that they should start the treatment for a better prognosis.

1.2 Research Objectives

1.2.1 Primary Objective

1) To describe the clinical manifestations of PWS patients, including the type of lesions and associated anomalies, as well as their relationship.

1.2.2 “Secondary Objective”

1) To study about the relationship between hypertrophic PWS with color, and location or sublocation of the lesion.

2) To study about the relationship between locations or sublocation that are related to specific anomalies in PWS patients.

1.3 Research Questions/ Assumptions

What are the clinical manifestations of untreated PWS patients, including the type of lesions and associated anomalies, as well as their relationship, from January 1, 2018-May 31, 2023 at the Institute of Dermatology, Thailand?

What is the relationship between hypertrophic PWS with color, and location or sublocation of the lesion?

What is the relationship between locations or sublocation that are related to specific anomalies in PWS patients?

1.4 Research Framework

Following posing a research question that can be answered, researcher need to ask for ethic committee approval in order to start collecting data to answer all the research questions in this retrospective study.

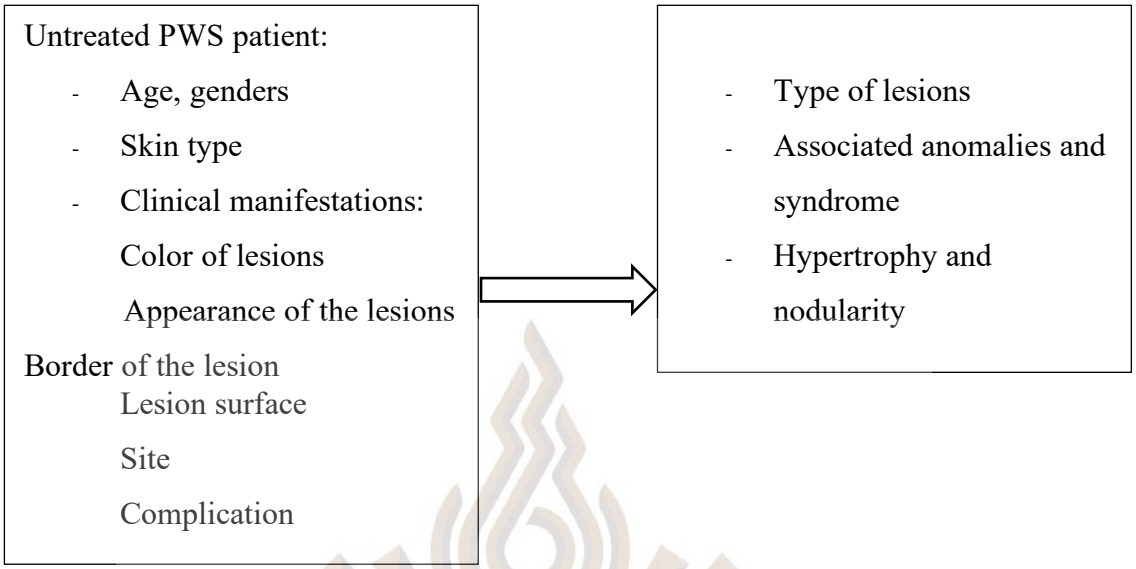

Figure 1.1 Research framework

1.5 Keywords

Port-wine Stains,
Capillary Vascular Malformation,
Vascular Birthmark.

1.6 Prospective results and worth of research outcome

The Institute of Dermatology is an institution that receives a large number and variety of PWS patients, especially as they age. The patient database, especially the pictures of patients, can be used to study. Therefore, it is expected that this research will provide the following data:

1.6.1 General information and clinical manifestations of PWS:

What are the most common ages, genders, and location for PWS visits to Institute of Dermatology, Thailand?

Which are the most characteristic of PWS visits to Institute of Dermatology, Thailand?

How is the youngest age to be found for hypertrophy or nodularity?

1.6.2 The analysis looked on clinical manifestations related to hypertrophy or nodularity, complications of the lesions, and anomalies and syndromes.

Which color of the lesions is related to hypertrophy, nodules, and complications?

Which location and sublocation are related to hypertrophy/nodularity, complications, and associated anomalies?

Which location or sublocation is related to specific anomalies e.g. glaucoma?

1.7 Definition of Terms

Capillary malformation (CM) "is classically a port-wine stain (PWS), low-flow lesions formed of dilated and ectatic capillaries and post-capillary venules that are mainly seen in the superficial papillary or reticular dermis. CM is present as pink to red macular patches that seem to get darker, redder to violaceous, the formation of blebs or hyperplastic, and is somewhat associated with soft tissue hypertrophy or bone overgrowth as the patient ages. CM do not vanish on their own.

Chapter 2

Literature Review

2.1 Port wine stains (PWS)

PWS are the second most common capillary malformations after nevus simplex [Figure 2.1].(Diociaiuti et al., 2021) PWS refers to vascular ectasias that have the potential to thicken over time. PWS manifests as a red mark, flat from birth, as pinkish or erythematous patches on the skin, and they may occasionally impact the mucosa. Because of the dilation of capillaries and postcapillary venules in the afflicted areas, the skin's hemoglobin concentration has increased, which is the cause of the color change to reddish or violaceous patches. It doesn't spontaneously regress. If left untreated, it could become thicker and darker in adulthood as a nodular thickening [Figure 2.2] or an accompanying pyogenic granuloma.(Brightman et al., 2015; Chang, Kim, & Lee, 2011; Faurschou et al., 2011; Rozas-Muñoz, Frieden, Roé, Puig, & Baselga, 2016)

PWS occur in up to 0.3% of newborns and often affect cosmetically sensitive areas such as the visage and neck, particularly the V1 and V2 dermatomes. However, the trunk and extremities are also typically affected. It may occasionally result in functional impairment as well.(Arisa et al., 2012; Brightman et al., 2015; Wanitphakdeedecha, et al., 2021) PWS should not only be considered as an aesthetic issue but also as an illness with seriously detrimental psychological effects. The negative response of people to a notable person has a negative impact on personality development in almost all cases. Due to the stigma and deformity associated with PWS caused by hypertrophy of underlying soft tissue and bone, which affects the facial features of many patients, patients experience low

self-esteem and psychological stress.(Augustin, Zschocke, Wiek, Peschen, & Vanscheidt, 1998; Slaughter, Chen, & Williams, 2016; Tark et al., 2011; Raath et al., 2021; Wassef et al., 2015) The social lives of adolescents and adults statistically show significant negative influences, while children with PWS are statistically show significant negative influences, while children with PWS are frequently discriminated against by their peers. (Wanitphakdeedecha et al., 2021)

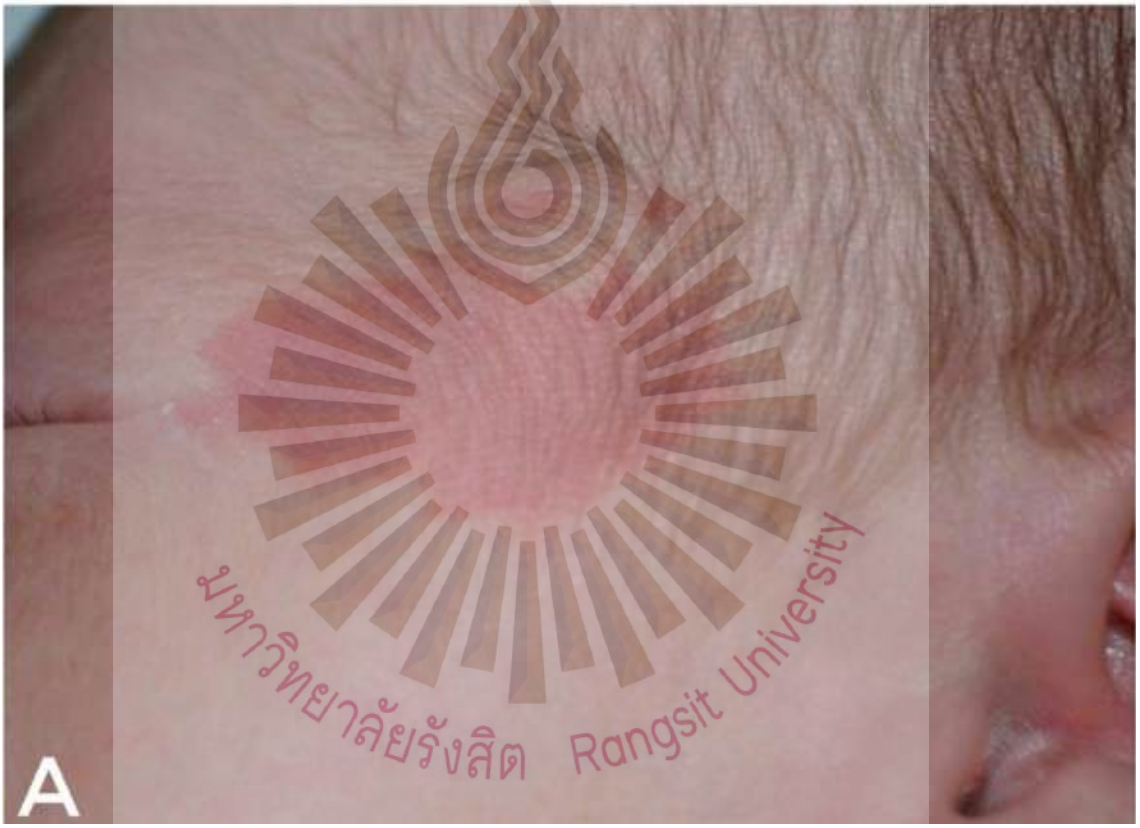

Figure 2.1 **“**Vascular Birthmarks”: (A) Capillary malformation (port wine stain)

Source: Diociaiuti et al., 2021

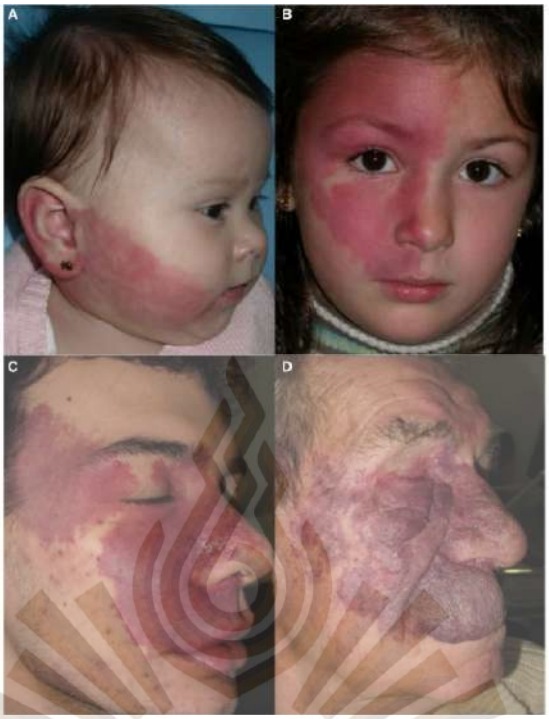

Figure 2.2 (A) PWS on the mandibular region. (B) wide spread PWS involved with the trigeminal nerve of the V1, V2 dermatomes. (C and D) PWS with progressive soft tissues hypertrophy.
Source: Rozas-Muñoz et al., 2016

2.1.1 Anatomic locations and Sex differences of PWS

Anatomic locations of PWS lesions

The PWS's location aids in clinical implementation prediction and the possibility of related abnormalities. PWS on the trunk and extremities are usually constant or lightening, whereas PWS on the face can become darker or violaceous over time.(Rozas-Muñoz et al., 2016) According to the location of the sensory trigeminal nerve, facial CM frequently occur in the regions of quasi-dermatomal such as V1 (ophthalmic region), which includes the upper eyelid and the forehead, V2 (maxillary region), and V3 (mandibular region). The head, face, and neck, especially the V1 and V2 dermatomes, are the most common presenting areas. The limbs and trunk are commonly impacted as well. As shown by research published by Lee JW et al. on 160 patients diagnosed with CM. The V2 is the

most frequently affected in terms of distribution (28%), followed by the V3 (16%), and the V1 (3%). The combined V1/V2 involvement is 24%, the V2/V3 involvement is 9%, and the V1/V2/V3 involvement is 11%. Among the subsites, upper lip growth was most noticeable (31%), then cheek hypertrophy (14%), and finally nose hypertrophy (12%). Eight individuals in the oral cavity showed gingival involvement, with five of them exhibiting gingival hypertrophy. Soft tissue hypertrophy was discovered in 82 % of nodular lesions [Figure 2.3, 2.4].(Lee et al., 2015) According to previous research by Enjolras, Riche, & Merland, 1985, 45% the population is confined to one of the three zones. In the other 55%, there are numerous dermatomes or the midline is crossed.(8) The mucous membranes are frequently directly affected. Even though the cutaneous staining is typically visible at birth, it can go unacknowledged since it is covered by the erythema of the newborn. The macules with a light pink color gradually darkened over time to take on the distinctive reddish-purple color. In some cases of PWS, hypertrophy of the soft tissue, bony hypertrophy progressively developed into nodule-cobblestone formation during late adult life.(Enjolras et al., 1985; Lee et al., 2015)

In the research by Shi et al. into 848 cases of PWS patients, 380 of the cases had more than two areas of the cutaneous lesions on their facial area, and the evaluations of pulse dye laser effectiveness, which differed in various parts of the face, were recorded. They classified those cutaneous lesions areas into eleven sites, including eight areas on the facial area, neck, trunk, and limbs, and reported the different effects from the highest to the worst according to those eleven locations. Among all regions, the temporal area had the highest impact to PDL, while the extremities had the worst impact. The effectiveness of PDL treatment on PWS patients was actually associated with these 11 locations, according to their analysis of the clinical data as shown in the Table 2.1. However, there was no significant difference in response to PDL between the temporal region, forehead region, chin region, or nasal region. But according to the data they received, there was a significant difference in response to PDL among PWS patients with other diverse locations of PWS lesions.(Shi et al., 2014)

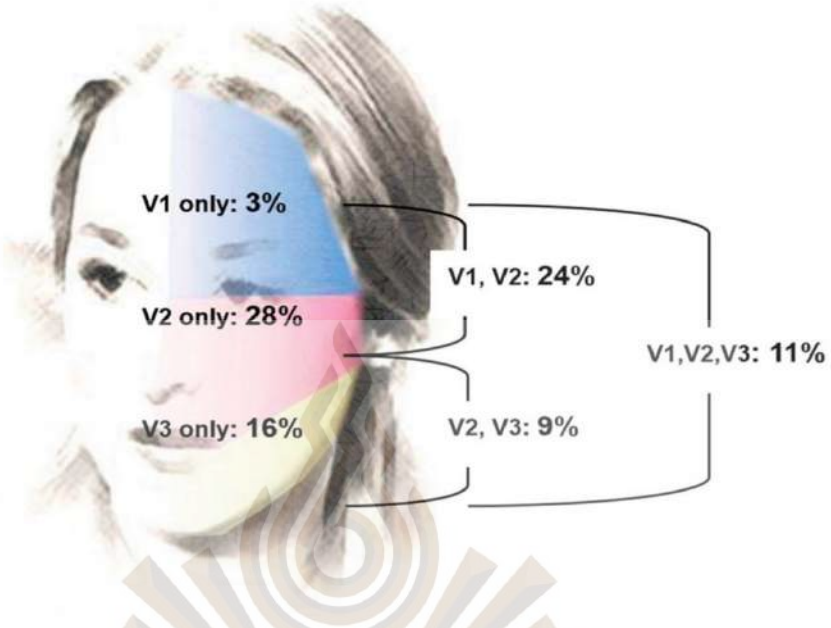

Figure 2.3 Soft tissues hypertrophy of Dermatome distribution.

Source: Lee et al., 2015

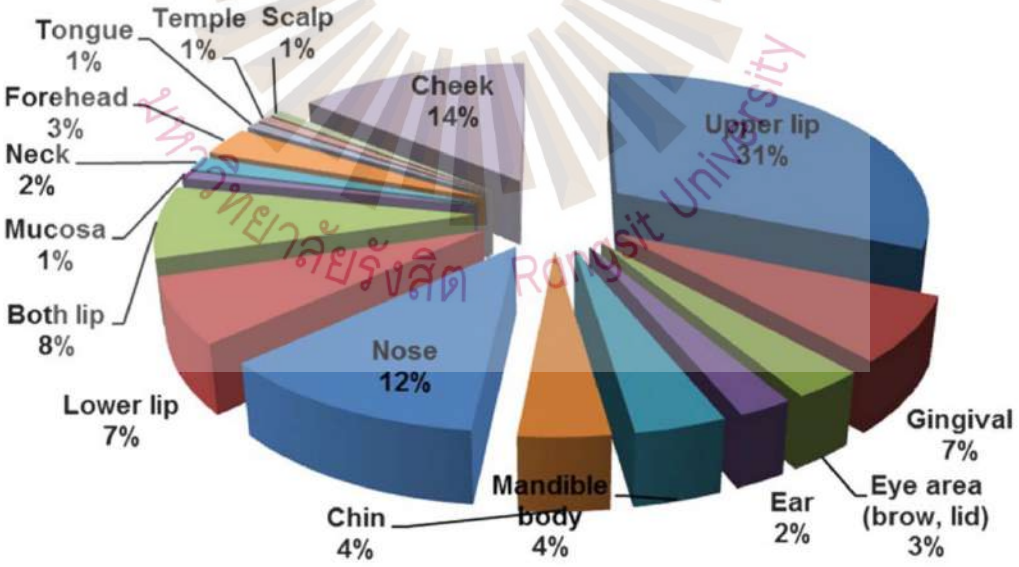

Figure 2.4 Anatomic distribution of soft tissue hypertrophy.

Source: Lee et al., 2015

Table 2.1 Physician global assessment with association with the different areas of lesions in PWS patients with their effectiveness of treatment, (number of patients [%]).

Position	**Number of patients**	**Cure**	**Significant improvement**	**Moderate improvement**	**Poor improvement**
Forehead region	80	5 (6.3)	7 (8.8)	47 (58.6)	21 (26.3)
Temporal region	105	9 (8.6)	18 (17.1)	63 (60.0)	15 (14.3)
Malar region	262	16 (6.1)	33 (12.6)	141 (53.8)	72 (27.5)
Buccal region	194	17 (8.8)	34 (17.5)	95 (49.0)	48 (24.7)
Chin region	84	3 (3.6)	10 (11.9)	46 (54.8)	25 (29.7)
Orbital region	67	2 (3.0)	11 (16.4)	31 (46.3)	23 (34.3)
Nasal region	64	4 (6.3)	7 (10.9)	37 (57.8)	16 (25.0)
Oral region	74	2 (2.7)	16 (21.6)	32 (43.2)	24 (32.5)
Neck	52	4 (7.7)	7 (13.5)	24 (46.1)	17 (32.7)
Body	30	3 (10.0)	3 (10.0)	13 (43.3)	11 (36.7)
Limb	45	3 (6.7)	3 (6.7)	14 (31.1)	25 (55.5)

Notes: The table shows the assessment of the treatment response by an independent dermatologist in charge. Cure =76%-100% skin recovery; significant improvement =51%-75% skin recovery; moderate improvement =26%-50% skin recovery; poor improvement =0%-25% skin recovery.

Source: Shi et al., 2014

Sex differences

From previous studies and literature reviews, many articles have stated that there is no sex preference in PWS patients. It affects males and females equally.(Brightman et al., 2015; Lam & Williams, 2004; Wanitphakdeedecha et al., 2021)

In the research of sex differences by Elias et al. about the isolated and those PWS associated syndromes, which involved the anatomic distribution, they also mentioned that there was no gender difference in the anatomic location of the lesions in both the isolated and associated syndromes.(Elias et al., 2021) The result of that research showed that there was a feminist majority of isolated PWS, with a total of 149 of 269 patients (54%) , with no statistical significance (P = 0.72). In SWS, the female preponderance was greater, 18 of 23 cases (78%), with statistical significance (P = 0.03). This gender distinction was not observed in the KTS subgroup, which comprised 84 of the 168 cases (50%) (P = 0.13). Among the 516 PWS patients, there were 234 (45.4%) men and 282 (54.6%) women to classify anatomic sites for analysis. There were 269 with isolated PWS (52%), 23 with Sturge-Weber syndrome (SWS) (4.5%), 168 with Klippel-Trenaunay syndrome (KTS) (32.6%), and 56 with various syndromes (such as Cobb syndrome, cutis marmorata telangiectatic congenita (CMTC), phakomatosis pigmentovascularis (PPV), Proteus syndrome, Beckwith-Wiedeman syndrome, Rubibstein-Taybu syndrome, Roberts syndrome, Coat disease, etc) is only 10.8%. As a result, they conclude that female individuals seem to be more prone to being identified as having SWS and are more likely to be approached in the Dermatology department for isolated PWS. Both isolated and syndromes associated with PWS, which either go beyond the midline or are bilateral, are considered proportionally of PWS. In all disease categories, extremity lesions are frequent. Both clinicians need to be mindful of the locational differences and the lack of laterality that both isolated and syndrome-associated PWS appear to be commonly manifested. They confirmed from their study that the forehead site is defined as a high-risk region for SWS (Table 2.2).(Elias et al., 2021)

Table 2.2 Demographics of Research Population of PWS-associated syndrome

	Syndrome				
	Isolated PWS	**KTS**	**SWS**	**Other**	**Total**
Sex (*P* = .04)	**n (col.%)**	**n (%)**	**n (%)**	**n (%)**	**(col.%)**
Female	149 (55.4)	84 (50)	18 (78.3)	31 (55.4)	282 (54.6)
Male	120 (44.6)	84 (50)	5 (21.7)	25 (44.6)	234 (45.4)
Total (row %)	269 (52.1)	168 (32.6)	23 (4.5)	56 (10.8)	

Note: Sex was analyzed across isolated and syndrome-associated PWS. Female predominance was observed in isolated, SWS and other subgroups.

Abbreviation: KTS,Klippel-Trenanuay syndrome; PWS, Port-wine stain; SWS, Sturge-Weber syndrome.

Source: Eilas et al., 2021

2.1.2 Natural history of PWS

PWS is progressive in nature and may gradually increase the thickness and the depth of color when the individual gets older, from light pink, red, or deep purple hue, finally altered to hypertrophic, bony hypertrophic, or nodule form. The cause of getting thicker with age is due to the correlation of continuation vascular ectasia, not because of hyperplasia or proliferative change. (Drooge, Beek, Veen, Horst, & Wolkerstorfer, 2012; Minkis, Geronemus, & Hale, 2009; Passeron et al., 2016; Prather & Arndt, 2015) In the cohort study by Drooge et al. about PWS hypertrophic prevalence and PWS characteristics, 335 individuals were identified as 20% of the patients having hypertrophy (distinguished by 5% thickened, 8% nodularity, and 7% of both characteristics).

Red is the most visible color in the hypertrophic area (50%), while purple is 44%. Hypertrophic in PWS is mainly seen in patients older than 40 years, and they only found 7% in younger individual (age less than 20years).(Drooge et al., 2012) In another publication by Lee JW et al. on 160 patients diagnosed with CM, 60% of patients (96

patients) indicated disease progression in the various forms of nodule development, soft tissue or bony hypertrophy. A group of 87 patients remained after limiting the study to individuals with previously untreated CM, 36 of whom were men (41%) and 51 of whom were women (59%). From 1 year until 29 years old, hypertrophy might start. Soft tissue hypertrophy typically starts at the age of nine. 38/87 (44%) of the patients with an average age of onset of 22 years (14-53years) had nodules, commonly known as cobblestones. Bony hypertrophy, which started on average at the age of 15 in twelve individuals (14%), was detected. According to sex distribution, female patients were twice as likely as male patients to develop bone hypertrophy. The most prevalent soft tissue hypertrophy in individuals with bone hypertrophy is the maxilla (V2), followed by the mandible (V3).(Lee et al., 2015) Most of the publications suggested all patients with PWS should avoid inadequate treatment (receive sufficient treatment and follow up with doctors) in order to get the maximal clearance of the lesions, as delay in treatment might lead to hypertrophic, bony hypertrophic, and nodularity, which might increase the risk for complications as PWS continues to progress without proper and adequate treatment [Figure 2.5].(Minkis et al., 2009)

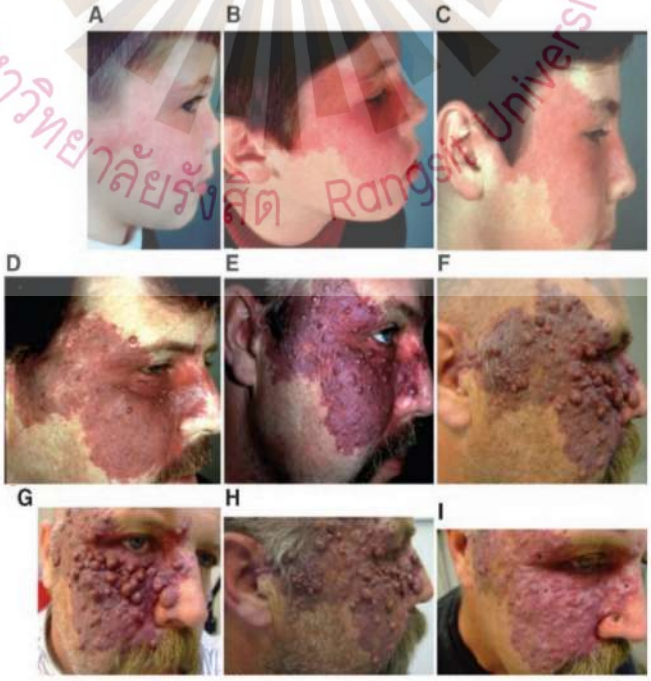

Figure 2.5 Port wine stain progression. **A–D:** The lesion of the patient appeared with bright pink color patch and plaque since birth and in childhood, developed into deep violaceous patch with nodularity association in his thirties. **E–G:** The lesion keeps developing into hypertrophy, darkening in pigments and continues increasing in nodularity (due to the inconsistent and inadequate treatment). **H-I:** The lesion improved after the patient received the effective treatment of using high energy PDL and the CO2 laser on the nodules.

Source: Minkis et al., 2009

2.1.3 Syndrome associated PWS

PWS do not subside by themselves; they grow in proportion to the individuals and may be correlated with syndromes such as Sturge-Weber syndrome (SWS), which is affected by first trigeminal division malformation with possible V2 or V3 engagement, central nervous system abnormalities, and glaucoma [Figure 2.6].(Han et al., 2020; Lam & Williams, 2004; Lee et al., 2015; Minkis et al., 2009; Rozas-Muñoz et al., 2016; Slaughter et al., 2016) The impairment in developing neural crest cell precursors has been found to be correlated with SWS embryological basics during the first embryological trimester. (Lambiase, Mantelli, Bruscolini, La, & Abdolrahimzadeh, 2016)

Klippel-Trenaunay syndrome (KTS) is characterized by unilateral malformation of the lower limbs with hypertrophy associated with lymphedema, varicose veins, and phleboliths. Occasionally, it is associated with progressive enlargement of the soft tissues or underlying bones [Figure 2.7]. Gingival hypertrophy and associated dental abnormalities are also conceivable [Figure 2.8]. (Han et al., 2020; Lam & Williams, 2004; Lee et al., 2015; Minkis et al., 2009; Rozas-Muñoz et al., 2016; Slaughter et al., 2016)

In Elias et al. studies, it was shown that anatomical locations differed predictably according to syndrome, with 91% of PWS in SWS mostly seen on the face and 9% of PWS on the face along with another site. 93% of patients with KTS had only body-specific

lesions, while 7% also had lesions on their faces. 96% of SWS patients had a lesion partially or entirely in the high-risk region of the forehead. The remaining lesion was in the mandible area and was not in the high-risk area on the front of the head. 20% of upper ex lesions and 82% of lower limb lesions made up the PWS caused by KTS. Lesions on lower extremities were more frequent in isolated PWS (91cases, around 34%) than upper limb lesions (47cases, around 17%) as shown in (Table 2.3). (Elias, Hand, Tollefson, & Davis, 2021)

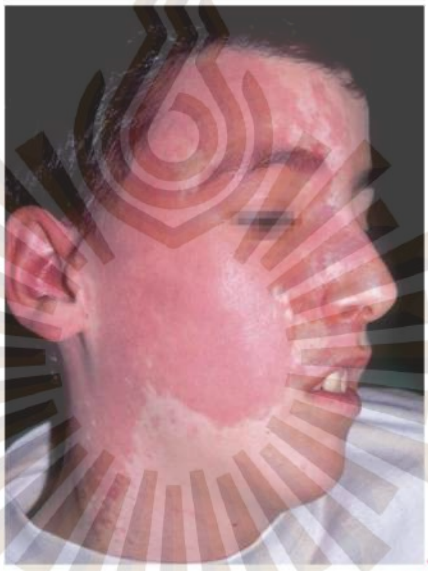

Figure 2.6 Port wine stains associated with SWS, involved with forehead region(V1), and V2, leptomeningeal, and glaucoma.
Source: Redondo, 2007

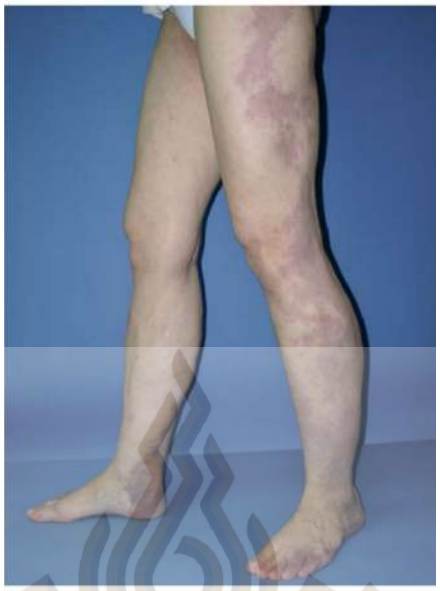

Figure 2.7 KTS: diffused PWS with irregular border with tenuous coloration of the external site of the legs.

Source: Redondo, 2007

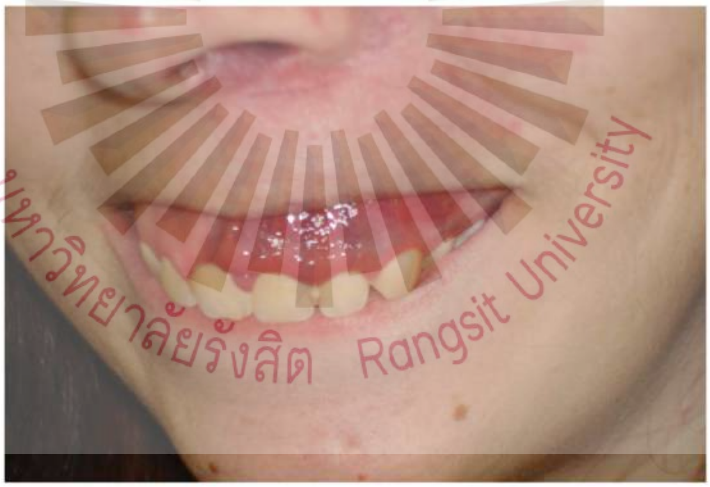

Figure 2.8 Gingival Hypertrophy.

Source: Lee et al., 2015

Table 2.3 Location of PWS with other syndromes associated PWS.

	Syndrome

	Isolated PWS	KTS	SWS	Other	Total
	n (col.%)	n (%)	n (%)	n (%)	(col.%)
Laterality (P =.04)					
Left	112 (41.6)	76 (45.2)	10 (43.5)	20 (35.7)	218 (42.3)
Right	113 (42)	61 (36.3)	6 (26.1)	24 (42.9)	202 (39.1)
Both	44 (16.4)	31 (18.5)	7 (30.4)	12 (21.4)	96 (18.6)
Anatomic location ($P \leq 0.01$)					
Face only	117 (43.5)	0 (0)	21 (91.3)	3 (5.4)	141 (27.33)
Limb only	94 (34.9)	81 (48.2)	0 (0)	23 (41.1)	198 (38.4)
Trunk only	20 (7.4)	9 (5.4)	0 (0)	4 (7.1)	33 (6.4)
Face and limb	3 (1.1)	3 (1.8)	1 (4.35)	1 (1.8)	8 (1.5)
Face and trunk	6 (2.2)	3 (1.8)	0 (0)	0 (0)	9 (1.7)
Limb and trunk	28 (10.4)	65 (38.7)	0 (0)	25 (44.6)	118 (22.9)

Table 2.3 Location of PWS with other syndromes associated PWS. (Cont.)

	Syndrome				
	Isolated PWS	KTS	SWS	Other	Total
	n (col.%)	n (%)	n (%)	n (%)	(col.%)
Face, limb, and trunk	1 (0.4)	7 (1.4)	1 (4.35)	0 (0)	9 (1.7)
Limb location (P = .02)					
Upper limb	36 (28.3)	19 (12.2)	1 (50)	10 (20.4)	66 (19.8)
Lower limb	80 (63)	124 (79.5)	1 (50)	34 (69.4)	239 (71.6)
Both	11 (8.7)	13 (8.3)	0 (0)	5 (10.2)	31 (8.68)
Total (row %)	269 (52.1)	168 (32.6)	23 (4.5)	56 (10.8)	

Source: Elias et al., 2021

Parkes-Weber syndrome is another one of the vascular malformation syndromes (venular arteriovenous malformation) that are rare and have occurred since birth. It

primarily affects the legs (77%) rather than the arms. Vascular anomalies in this syndrome are characterized by fast flow vascular lesions, less likely to an extent compared to KTS. Increasing cardiac load is the most common complication, which could result in cutaneous ischemia and heart failure. (Jean, Julie, & Lorenzo, 2018; Redondo, 2007)

Phakomatosis pigmentovascularis (PPV) is a very uncommon cutaneous vascular malformation that cohabits with pigmentary nevus. PPV is diagnosed by clinical picture of individual cutaneous syndromes, significantly presented as a nevus anemicus. Various authors have discovered those associated with PPV and isolated nevi flammeus differences. In the absence of systematic complications, PPV does not require any further treatment.

Diffuse capillary malformation with overgrowth (DCMO) is a common reticulated CM accompanied by proportionate bone hypertrophy and/or soft tissue. Even though DCMO individually has noticeable subcutaneous veins in clinical presentation, DCMO does not coexist with either real venous malformation or lymphatic malformation. Furthermore, neurological impairments are not linked to DCMO and macrocephaly-CM (MCM) patients. The overgrowth in DCMO is not progressive, nor does it connect to the site of the CM, which is different from KTS. (Jean et al., 2018)

Macrocephaly-capillary malformation (MCM) or megalencephaly-CM is also a common reticulated capillary malformation, presenting with asymmetrical overgrowth progressively of unilateral megalencephaly. Other clinical manifestations include frontal bossing, hypotonia, late in development, syndactyly, and nevus simplex of the mid-face. (Jean et al., 2018)

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome is the most common with macrocephalic and malignant development, occurring most commonly in the thyroid, breast, and endometrium. Cutaneous features are seen with partially hyper-

vascularized fat, vascular malformation, and genital pigmented macule. (Jean et al., 2018; McCuaig, 2017)

Congenital lipomatous overgrowth, vascular malformations, epidermal nevus, spina/skeletal anomalies/scoliosis syndrome (CLOVES) is a progressive and asymmetrical infiltrative lipomatous overgrowth, commonly truncal, epidermal nevi, vascular anomalies, scoliosis, or skeletal problems, which can be characterized by broad feet and hands, seizures, and spinal arteriovenous defects. The clinical presentation of CLOVES, KTS, and MCM can overlap sometimes. (Jean et al., 2018)

2.1.4 Pathogenesis

Most vascular stains have an unclear pathogenesis, but specific genetic discoveries have revealed various clues. The embryological process of vasculogenesis, which occurs first, and generates the primitive vascular plexus. The majority of blood and lymphatic arteries are then created by angiogenesis, the secondary sprouting of endothelial cells derived from mesoderms. Capillaries, veins, and arteries are generated by endothelial differentiation, recruitment of smooth muscle cell precursors to sheath endothelial cells and construct vessel walls, and eventually, changes in channel size, shape, and rheology. A great variety of common disorders known as vascular malformations are caused by modifications in how blood or lymphatic channels develop. When the signaling pathway which is responsible for migration regulation, adhesion, maturation, differentiation, and survival of the cells of vascular walls is not functioning, it is believed that the pathogenic role has occurred.

Vascular malformations do not cause the increase in cellular proliferation markers. Mural cells in the cephalic area of the embryo are associated with endothelial cells from the neural crest. Consequently, a vascular malformation complex involving the head, such as SWS, could be the result of a somatic mutation in the embryo's anterior neural crest or surrounding cephalic mesenchyma. The genetic abnormalities causing diverse vascular

malformations have shed light on regulatory pathways which are very essential to vascular morphogenesis. Somatic mutations in different or the same genes may result in sporadic vascular malformations more than those involved in the less common familial types of the same kind of malformation. (Jean et al., 2018; Rozas-Muñoz et al., 2016)

PWS is now recognized as being caused by somatic mosaic mutations in genes that affect cell-cycle regulation, including the GNAQ gene (on chromosome 9), GNA11, PiK3CA, and others involved in cell-cycle signaling. Because these genes share carcinogenic pathways that result in synchronous, tightly controlled cellular proliferation and growth, this discovery has altered our fundamental understanding of their pathophysiology.(Lee & Chung, 2018; Rozas-Muñoz et al., 2016; Tran et al., 2021) GNAQ and GNA11 are the most common somatic activating mutation. From [Figure 2.9], the clinical features in this patient with GNAQ mutation have shown that facial PWS lesions have covered most of the left side of the face, which is involved in V1 regions, and might also have an ocular involvement and an increased risk of SWS. While this GNA11 mutation patient manifested by light pink-red, finely reticulated stains with poorly differentiate borders. (Jean et al., 2018; Siegel et al., 2018; Tran et al., 2021) PWS can be isolated or combined with other syndromes, such as SWS, PPV, or PiK3CA-related overgrowth syndromes (PROS). While exact mechanisms for the most prevalent mutations in vascular stains (GNAQ, GNA11, and PiK3CA hot spot) are not yet known, causal gain-of-function somatic mutations have been identified. Causative gain of function somatic mosaic mutations may explain the gradual development of nodularity, soft-tissue hypertrophy, and secondary vascular alteration in PWS.(Lee & Chung, 2018; Rozas-Muñoz et al., 2016; Tran et al., 2021)

The pathways of intracellular signaling in Figure 2.10 are involved in vascular staining. They have explained that PWS and SWS might be caused by GNAQ mutations in the pathway of G protein-coupled receptor (GPCR). In this pathway, there is an activation of the G protein alpha subunit, including GNAQ, which is activated by the

binding of GPCR and other different ligands such as endothelin or vasopressin. GTP is hydrolysed by GNAQ and then converted into inositol 1,4,5-triphosphate (IP3) and activating membrane diacylglycerol (DAG) by activation phospholipase Cb (PLC-b). DAG activated the Raf-MEK-ERK pathway (Raf, MAP 2K 1/2, MAPK3) through activation of protein kinase C (PKC). KTS, CLOVES syndrome, or megalenecephaly-capillary malformation, could be the result of various PIK3CA mutations, including PIK3CA, AKT, and mTOR by receptor tyrosine kinase activation. Parkes-Weber syndrome and CM-AVM may be caused by RAS mutations, as the low molecular weight G protein Ras is activated by receptor tyrosine kinase, which also activates Raf, MAP 2K 1/2, and MAPK3.(Rozas-Muñoz et al., 2016)

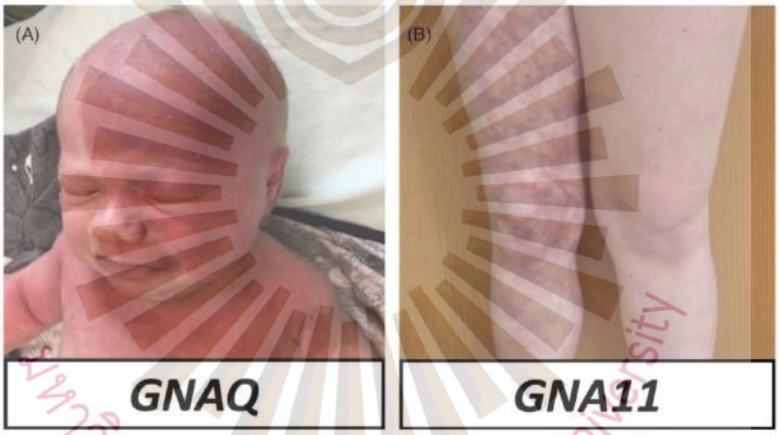

Figure 2.9 The most common mutations in vascular malformations of Genotype-phenotype correlation.

Source: Tran et al., 2021

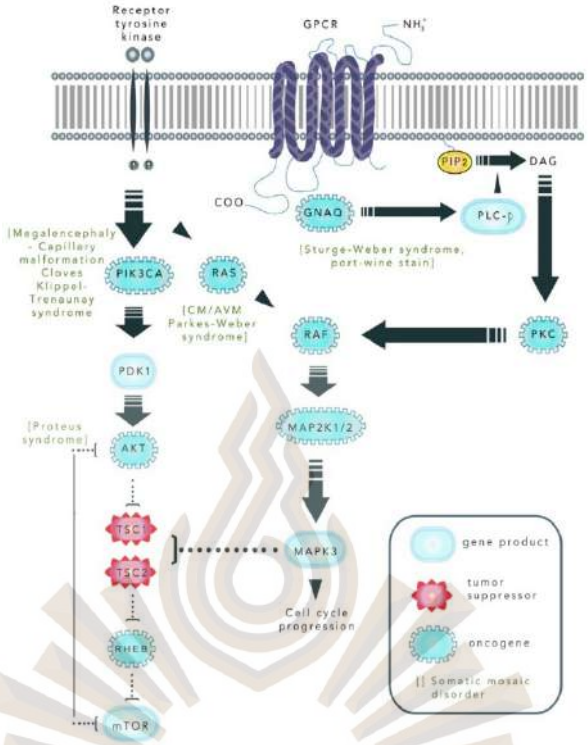

Figure 2.10 Intracellular signaling pathways involved in vascular stains. Mutations in GNAQ may produce port wine stains and Sturge-Weber syndrome .

Source: Rozas-Muñoz et al., 2016

2.1.5 Investigation

Vascular malformations are significantly diagnosed by the clinical manifestation of the lesions. However, it has been discovered that some individuals with vascular abnormalities who attended the referral clinics were not able to identify the diagnosis properly since some of these vascular lesions initially appeared to be very similar. It is absolutely essential to identify and differentiate each lesion, such as PWS and infantile hemangioma, as these abnormalities require different course of treatment. Further investigations of vascular malformation include histopathology, imaging, and genetic testing.(Kang et al., n.d.; Piccolo et al., 2018; Redondo, 2007)

Histopathology

The capillary malformation is defined histologically by the initially appearance of a normal capillary network, then gradually becoming dilated capillaries of the papillary and upper reticular dermis, together with the regions that have an increased number of normal-appearance capillaries. Fibronectin, factor VIII, and basement membrane protein are intact. Endothelial cells are flattening. Positive S100 staining indicates defective innervation.(Kang et al., n.d.; Lee & Chung, 2018) Histopathological examination in Rao et al.'s article has shown the result of PWS biopsy as the scattered dilated blood vessels along with blood components and proliferative endothelial in the dermis and in the intervening stroma as shown in Figure 2.11.(Rao et al., 2020)

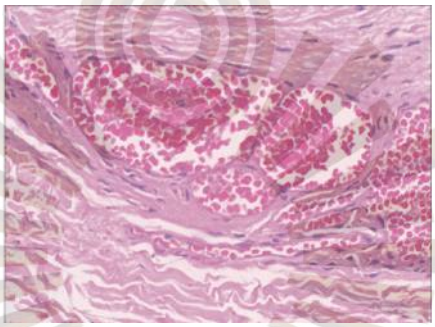

Figure 2.11 Port wine stain: Histopathology examination.

Source: Rao et al., 2020

Imaging studies

In most cases, imaging studies in CM are not required. However, in some rare cases, such as proliferation hemangioma, arteriovenous malformation, and Parkes-Weber syndrome, doppler ultrasound may be required to differential diagnosis from other situations. A neurologic and ophthalmologic investigation is required in cases of capillary malformation involved in some regions such as the fronto-palpebral, particularly the upper eyelid (inner part). Magnetic resonance imaging of the brain is suggested in the leptomeningeal congenital vascular malformation association. CM-AVM should be investigated with magnetic resonance imagining (MRI) of the spine and brain.(Kang et al., n.d.)

Dermoscopy

Dermoscopic findings are very useful in CM, as they can be used to determine the depth of vessels. The clinical appearance of CM is influenced by the depth and size of the vessel. Brightly colored lesions are mostly made up of ectatic superficial vessels. Contrarily, purple lesions develop from larger, deeper arteries, whereas pale pink lesions are mostly made up of deeper, smaller ectatic vessels. Red dots (dotted vessels), clods (milky-red globules), and linear vessels are the three primary morphologic forms of vessels, which can be seen in dermoscopy. The dermoscopic features are divided into two main types, including red globules as type I lesions and prominent red lines as type II lesions. Red globules in the papillary dermis represent ectatic, vertically positioned capillaries, whereas strong red lines in the reticular dermis reflect deeper, ectatic, horizontal capillaries. They discovered that type I lesions, which on dermoscopy showed a superficial pattern (red dots and globules as in Figure 2.12), responded effectively to laser therapy. However, the unsatisfactory response to laser therapy patterns was one of these patterns. The first pattern featured white linear streaks with a rose, white, or blue background, as shown in Figure 2.13, whereas the second pattern included light circular areas surrounding a central brownish dot [Figure 2.14]. So, dermoscopy is really useful as it could predict the patient outcome of laser therapy by differentiation the depth of the lesions.(Grazzini et al., 2012; Haliasos et al., 2013; Hsiao & Chang, 2011; McCuaig, 2017; Piccolo et al., 2018; Zhang et al., 2022)

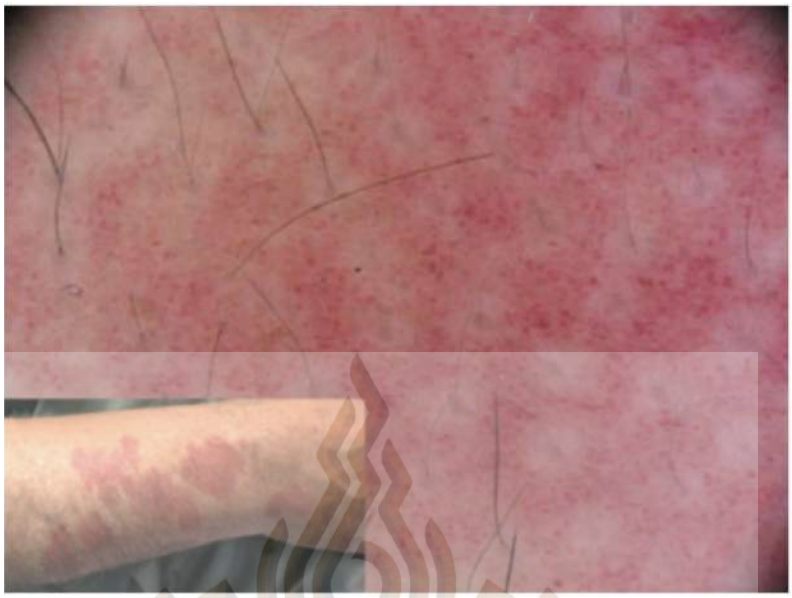

Figure 2.12 Dermoscopic feature of type I lesion in PWS.

Source: Haliasos et al., 2013

Figure 2.13 Dermoscopic feature of type II lesion in PWS (pattern1).

Source: Haliasos et al., 2013

Figure 2.14 Dermoscopic feature of type II lesion in PWS (pattern2).
Source: Haliasos et al., 2013

Genetic testing

Genetic testing could lead to recognition of the primary pathogenic pathways involved, such as somatic mosaic mutations in genes discovered to be the cause of PWS, which are involved in cell-cycle modulation, such as the GNAQ gene, GNA11, PiK3CA, catalytic subunit alpha, and other associated cell-cycle pathways. Genetic testing in CM is recommended, specifically in patients present with multifocal lesions. RASA1 and EPHB4 should be investigated in patients with CM-AVM (associated in multifocal lesions), as it could lead to intracerebral fast-flow lesions risk. The PROS tend to involve DCMO, CLOVES syndrome, CLAPO syndrome (Capillary malformation of the lower lip, Lymphatic malformation predominant on the face and neck, Asymmetry, and Partial/generalized Overgrowth), KTS, and MCM. (Diociaiuti et al., 2021; Jean et al., 2018; Kang et al., n.d.)

2.1.6 Management

PWS are vascular ectasias that can develop with age. According to the majority of studies, PWS are persistent and will not disappear on their own. It is possible that it will

acquire an overall thickening of the lesions and distinct nodules as it ages.(Brightman et al., 2015; Faurschou et al., 2011; Ortiz & Nelson, 2012; Yang et al., 2015) It can possibly cause functional impairment as well. (Brightman et al., 2015; Ortiz & Nelson, 2012; Wanitphakdeedecha et al., 2021)

Despite the availability of numerous treatment techniques such as cosmetic concealment, ionizing radiation, skin grafting, cryosurgery, dermabrasion, tattooing, and electrotherapy in previous decades, these treatments did not enhance cosmetic outcomes.(Cao et al., 2019; Jasim & Handley, 2007) Argon, Krypton, frequency-doubled Neodynium-doped:yttrium-aluminium-garnet (Nd:YAG), Potassium Titanyl Phosphate (KPT), Copper bromide, Alexandrite, Diode, long pulsed Nd:YAG, intense pulsed light (IPL), photodynamic treatment (PDL), and pulsed dye laser (PDL) have all been established to treat the vascular component of the lesions.(Brightman et al., 2015; Gemert et al., 1997; Jasim & Handley, 2007)

Argon, Krypton, and copper bromide (first generation laser) are suitable for skin phototypes I-III, and they are not convenient to use anymore, as the scarring rate is rising. Frequency-doubled Nd:YAG (532nm) is suitable for skin phototypes I-III too, but the devices have contact cooling, and can be considered as an initial treatment for resistant and residual CM. Both Alexandrite and Diode use cryogen spray cooling techniques, but Alexandrite is more commonly used for dark or resistant CM, whereas Diode is more commonly used for venous lakes, hair removal, or endo-venous ablation. Nd:YAG with 1064 nm wavelength is very convenient for dark skin phototypes as it is suitable for all skin phototypes (I-VI). It is suitable for dark or resistant CM, but as the depth of penetration is increased, it could lead to scarring and ulceration risk too. IPL and PDT are not commonly used in previously untreated CM, and IPL is less effective than laser treatment. The PDL,which is suitable for skin phototypes I-IV and has a wavelength range of 585-595 nm and is created with cryogen spray cooling, is the most convenient laser that has

been studies and widely use when compared to the others light source mentioned above [Table 2.4].(Brightman et al., 2015)

Among these laser treatments, PDL is the most widely used and most highly researched. Until recently, PDL has been used as the gold standard therapy for PWS. (Brightman et al., 2015; Tran et al., 2021; Raath et al., 2021)

Shi et al.'s article, published about the study of PDL efficacy applied to 848 patients diagnosed with PWS without a history of treatment with PDL. The range of PDL treatment numbers was between 3 and 20 times (mean 6.2±3.8). They used the physician global assessment to classify the response rate by "poor improvement" (0–25% skin recovery), "moderate improvement" (26–50% skin recovery), "significant improvement" (51–75% skin recovery), and "cure" (76–100% skin recovery). The result of their study is that 6.3% is "cure" (53/848 patients), 12.9% is "significant improvement" (109/848 patients), 50.7% is "moderate improvement" (430/848 patients), and 30.1% is "poor improvement" (256/848 patients).(Shi et al., 2014)

In Ho et al.'s studies, the result is not much different, but no one has complete clearance in their studies; only 23% got more than 50% clearance, 41% of them got 25-50% clearance, and more than 60% of the patients were found to have more than 25% clearance.(Ho et al., 2002) Early and effective therapy actually results in improvements of between 80% and 90%. Antiangiogenic medications, PDT, and other techniques to target dilated capillaries and limit revascularization after laser therapy are expected to improve PWS clearance. Innovations in epidermal protection techniques and laser technology will also enable more thorough outcomes to be achieved with lower chances of pigmentary alterations or scarring.(Brightman et al., 2015)

According to the study by M.I Van Raath et al., treatment outcomes for PWS have not improved over the last three decades (from 1986 to 2018). Despite numerous

technological and pharmacological advances, no novel therapeutic strategies for eliminating all PWS have been successful.(van Raath et al., 2019) However, recent research by Kiem Pham Cao in 2019 claimed that the anatomical evaluation of PDL on Vietnamese patients was satisfactory, with good results as, 43.8% of excellent responding (76-100% lightening), 18.8% of good responding (51-75% lightening), 18.8% of fair responding (26-50% lightening), and 18.8% of no responding (0-25% lightening).(Cao et al., 2019) In this investigation, 42 patients were given four test patches with varying fluences (11, 11.5, 12 and 12.5 J/cm2), pulse length (1.5 ms), and spot size (7 mm). In eight weeks, they select one of the four best results as the next therapy. They discovered that 595 nm PDL confirmed therapy effectiveness while causing no major side effects on their patients.(Cao et al., 2019)

Practicians have to know all the contributing factors that caused the resistant to treatment in order to maximize the effectiveness of the clearance. Recalcitrant conditions of individuals should be addressed, including age of patient, size of lesion, anatomical characteristics of the lesion, thickness of the skin, characteristics of vessels (depth, diameter and wall thickness), and the number of treatments received. As in Figure 2.15, it has been shown that starting the treatment prior to 1 year of age result in more than 30% lesion clearance compared to starting it at an older age, which could achieve 18% only. Moreover, in the case of being treated before 6 months old, Chapas et al. published that the percentage of average clearance could reach 88.6%, which is very high (Chapas, Eickhorst, & Geronemus, 2007; Morelli, 1995; Savas, Ledon, Franca, Chacon, & Nouri, 2013; Tran et al., 2021) The size of the lesion has also been studied as lesions smaller than 20cm^2 are involved in better responses of treatment (67% after 5 sessions of treatment), while lesions bigger than 40cm^2 respond only to 23%. Lesions in the center of the forehead responded best after five treatments, with the possibility of complete clearance. While the central face responded with 48% of clearance only. Other PDL-resistant factors are skin thickness (characterized by hypertrophy or nodularity), depth of vessels > 400 μm, diameter of vessels < 40 μm, and effectiveness of PDL to the lesion is decreasing after receiving more

than 5 sessions of treatment (the first 5 sessions was 55% of clearance, while the second 5 sessions responded only 18%).(Savas et al., 2013; Tran et al., 2021)

Table 2.4 Port wine stains treatment with vascular selective lasers

Laser/light source	**Wavelength (nm)**	**Epidermal cooling mechanism**	**Skin phototypes**	**Comments**
Argon	488-514	None	I-III	First-generation laser; increased rate of scarring; has largely fallen out of use
Krypton	520-530	None	I-III	First-generation laser; increased rate of scarring; has largely fallen out of use
Frequency-doubled Nd:YaG; potassium titanyl phosphate	532	Contact cooling or other	I-III	Studied primarily for resistant and residual CMs; can represent initial treatment choice
Copper bromide/ copper vapor	578	None	I-III	First-generation laser; increased rate of scarring; has largely fallen out of use

Table 2.4 Port wine stains treatment with vascular selective lasers (Cont.)

Laser/light source	**Wavelength (nm)**	**Epidermal cooling mechanism**	**Skin phototypes**	**Comments**
Pulsed dye laser (PDL)	585-595	Cryogen spray cooling	I-IV	Most commonly used and most well studied; gold standard for pediatric vascular birthmarks
Alexandrite	755	Cryogen spray cooling	I-IV	Primarily for dark or resistant CMs
Diode	800-940	Cryogen spray cooling and other	I-IV	May be used for CMs; more common for hair removal, venous lakes, endovenous ablation
Nd: YAG	1,096	Cryogen spray cooling	I-VI	Primarily for dark or resistant CMs; increased penetration depth; less absorption by melanin; increased risk of ulceration or scarring

Table 2.4 Port wine stains treatment with vascular selective lasers (Cont.)

Laser/light source	**Wavelength (nm)**	**Epidermal cooling mechanism**	**Skin phototypes**	**Comments**
Intense pulsed light	390-1,200; modifiable using filters	Variable; gel	I-IV	Less effective than laser treatment; may be preferred by patients for non-purpuric treatment
Photodynamic therapy	Varies; optimally matched to photosensitizer peak absorption wavelength	Typically not needed; fan optional	I-VI	Less commonly used; typically intravenous injection of photosensitizer with photosensitivity persisting for days to weeks; good-to-excellent results when compared to PDL

Abbreviations: CM, capillary malformation; Nd: YAG, neodymium-doped yttrium aluminum garnet; PDL, pulsed dye laser.

Source: Brightman et al., 2015

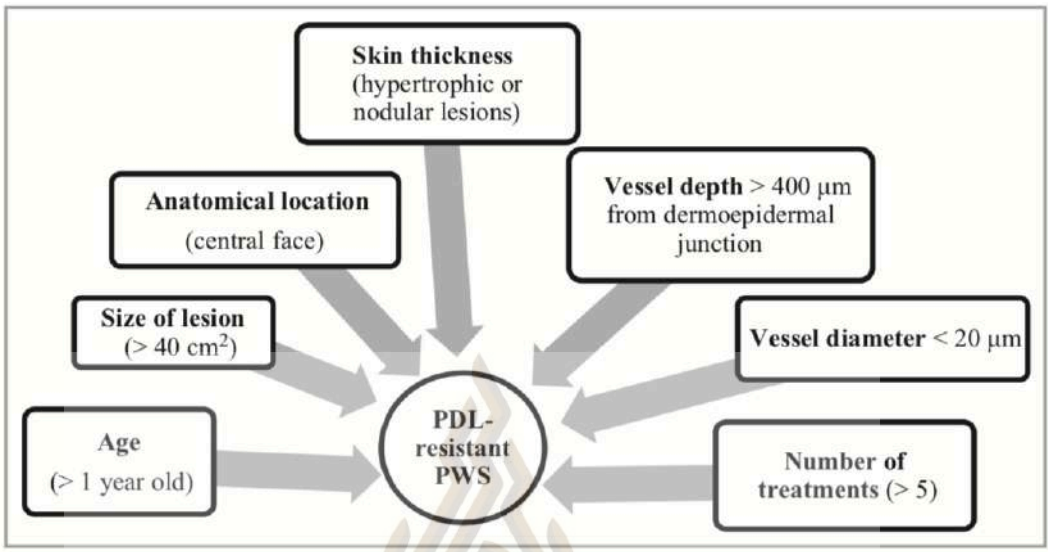

Figure 2.15 Contributed factors to Pulsed dye laser resistant in PWS.

Source: Savas et al., 2013

Chapter 3

Research Methodology

3.1 Population and Samples

We included port wine stains (PWS) patients who were diagnosed from January 1, 2018- May 31, 2023 at the Institute of Dermatology, Thailand. There were 182 patients diagnosed with PWS, previously untreated found after searching information from a database at the Institute of Dermatology, Thailand. There were 47 cases with insufficient data. So, the patient that is available in our research is approximately 135 cases.

3.2 Selection Criteria

3.2.1 Study population

All of previously untreated PWS patients who were diagnosed from January 1, 2018- May 31, 2023 at the Institute of Dermatology, Thailand.

3.2.2 Inclusion criteria

Previously untreated PWS patients who were diagnosed from January 1, 2018- May 31, 2022 at the Institute of Dermatology, Thailand.

Male and female patients of all ages

3.2.3 Exclusion criteria

Patients with insufficient data, such as unclear or missing photograph

Photographs that is not clear

3.3 Research Site

Institute of Dermatology, 420/7 Ratchawithi Road, Thung Phaya Thai, Rachathewi, Bangkok 10400

Telephone: 095-207-2811, 095-207-2812

3.4 Factors contributing to research

Support of patient information from the database of the institute of Dermatology and the availability of research resources that can provide necessary information for research.

Supervisor, teachers, consultants, and statistical personnel who can assist and advise on these research projects.

3.5 Methods of conducting research and place of testing/ data collection

3.5.1 Research model

Retrospective descriptive study

3.5.2 Research procedures

Examine the literature on PWS, including clinical patterns, anatomic locations, natural history, and management from PubMed, Cochrane, NCBI, and other search engines.

Collecting data for research questions and designing a case report form for the research process.

The researcher submits a proposal to the Institutional Review Board of the Institute of Dermatology and Department of Medical Services, Ministry of Public Health, Thailand

To search for information from the database of the Institute of Dermatology over 5 years (January 1, 2018- May 31, 2023) in patients diagnosed with PWS and meet the criteria for selecting patients to participate in the research project.

The history will be collected for patients who meet the inclusion criteria. Patients' demographic data, such as age, gender, and general health condition, were recorded. We will collect data on the clinical manifestation of each patient at the date of diagnosis and also other diseases associated in some cases.

The results will be analyzed of clinical manifestations of port wine stain of all subjects.

3.5.3 Consent procedure for volunteers

We can waive consent because this research is retrospective, followed by a recommendation for statistical consultation.

3.6 Collection of information

The history will be collected for selected patients by the inclusion and exclusion criteria.

Patients' demographic data, such as age, gender, and skin type were recorded.

We will collect data on the clinical manifestation of each patient at the date of diagnosis and also other diseases associated in some cases.

The information was collected using a case record form that did not include the patient's name and surname.

Data will be maintained in an electronic database with a password to prevent anyone from accessing it, or all papers will be preserved in a locked cabinet with the key held by the researcher.

3.7 Data Analysis and statistics used in data analysis

3.7.1 Descriptive statistics

For descriptive analysis included mean, standard deviation, frequency, and percentage.

3.7.2 Analytic statistics

For categorical data: Chi-square test and Fisher's Exact test were employed to analyze the variables and examine the relationships within hypertrophic PWS, the color of the lesion, and locations.

Data analysis will be used in SPSS version 26.0 program (IBM corporation) and defined as Statistical significance at 0.05 (p-value<0.05).

3.8 Prospective results and worth of research outcome

The Institute of Dermatology is an institution that receives a large number of PWS patients. The patient database obtained, especially photographs of patients, can be used to analyze the clinical manifestations of PWS. Therefore, it is expected that this research will be able to analyze the results and will be useful in planning the appropriate care of PWS patients with broader and more comprehensive information.

Chapter 4

Research Results

4.1 Demographic data and Clinical manifestation of PWS

Our objective of this retrospective study is to describe the clinical manifestations of PWS patients, including the type of lesions and associated anomalies. This study was conducted among 182 Port wine stain patients. The patients who have no photographs of lesions were 47 persons. Thus, a total of 135 PWS patients were included. The age of participants had an average of 27.11 years (age range: 1 to 66 years). More than half of the participants were females (55.6%). Considering their skin type, type III was the most common skin type (48.9%), followed by type IV (28.1%), and type II (12.6%). The mean of lesion onset was 0.11 ± 0.97 years. The clinical manifestations were presented in Table 4.1 The face was the most common location (58.5%). Majority of the patients, 63.7%, had red color of the lesion followed by purple and pink color (33.3% and 3%, respectively), as shown in Figure 4.1. With 68.9% of homogeneous appearance, while the majority of lesions were flat (68.9%), while 20.0% were hypertrophic and 10.4% were nodule. Figure 4.2 illustrates about the different age groups between hypertrophic and nodular lesions of PWS significantly (P-value = 0.022). Hypertrophic PWS patients had the highest proportion in the age range of 11-20 years (29.6%) whereas Nodule PWS patients had the highest proportion in the age range of 31-40 years (53.8%). Border of the lesion among those patients was found that 80% had well-defined and 20% had ill-defined. About 68.9% were less than 50% of lesion surface. Nearly one-third (31.9%) had V2 location and 48.9% had right site. The majority of complications of those patients were bleeding (3.7%), ulceration (2.2%), and pyogenic granuloma (1.5%). The sublocations of the lesion among

135 PWS were shown in Table 4.2. Upper eyelid (17.8%) was the most common sublocation, followed by neck (17.0%), upper lip (16.3%) and arm (11.1%).

Table 4.1 Number and percent of the clinical manifestations among 135 PWS patients

Clinical manifestations	**Number**	**%**
Color of the lesions		
Pink	4	3
Red	86	63.7
Purple	45	33.3
Appearance of the lesions		
Homogeneous	93	68.9
Heterogeneous	42	31.1
Symmetry	2	1.5
Asymmetry	133	98.5
Flat	94	68.9
Hypertrophic	27	20
Nodule	14	10.4
Border of the lesion		
well-defined	108	80
Ill-defined	27	20
Lesion surface		
<50% of each location	93	68.9
>50% of each location	42	31.1
Site		
Left	52	38.5
Right	66	48.9
Midline	17	12.6

Table 4.1 Number and percent of the clinical manifestations among 135 PWS patients (Cont.)

Clinical manifestations	Number	%
Color of the lesions		
Complications		
Bleeding	5	3.7
Ulcer	3	2.2
Pyogenic granuloma	2	1.5

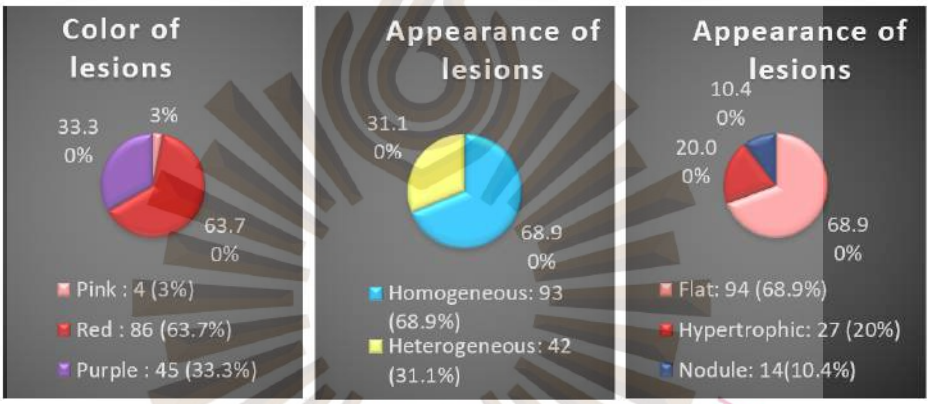

Figure 4.1 Color and Appearance of PWS lesions

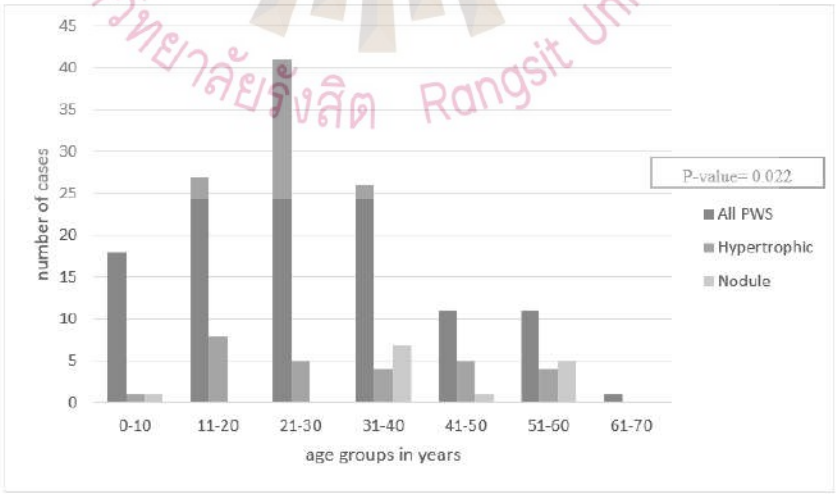

Figure 4.2 Different age groups of PWS patients and types of PWS

Table 4.2 Number and percent of the sublocations for the lesions among 135 PWS patients

Sublocation	**Number**	**%**
Face*	79	58.5
V1	33	32.7
V2	43	42.6
V3	25	24.7
Upper eyelid	24	17.8
Lower eyelid	11	8.1
Upper lip	22	16.3
Lower lip	6	4.4
Oral mucosa	6	4.4
Scalp	10	7.4
Temporal	4	3
Occipital	6	4.4
Neck	23	17
Anterior	5	3.7
Midline	0	0
Lateral	18	13.3
Trunk*	15	11.1
Anterior	12	8.9
Posterior	2	1.5
Midline	4	3
Lateral	11	8.1
Arm*	15	11.1
Proximal	8	5.9
Distal	9	6.7
Forearm*	11	8.1

Table 4.2 Number and percent of the sublocations for the lesions among 135 PWS patients (Cont.)

Sublocation	Number	%
Proximal	6	4.4
Distal	9	6.7
Thigh*	4	3
Proximal	3	2.2
Distal	1	0.7
Leg*	11	8.1
Proximal	6	4.4
Distal	8	5.9
Hand	3	2.2
Dorsal	2	1.5
Ventral	1	0.7
Foot*	2	1.5
Dorsal	2	1.5
Ventral	1	0.7

*Multiple sublocation involvement for 1 patient

4.2 The relationship between hypertrophic PWS with color, location, and sublocation of the lesion

Another objective of our study is to find the relationship between hypertrophic PWS, color, and the location or sublocation of the lesions, as shown is Table 4.3, It was found that the red and purple colors of the lesion were significantly related to hypertrophic PWS (p-values 0.001 and 0.003 respectively). The purple color had a proportion of hypertrophic PWS, 63.0%, higher than those without. Significant differences were observed in hypertrophic PWS concerning V3, upper lip, lower lip, and oral mucosa sublocations (p-values of 0.006, 0.003, 0.015, and <0.001, respectively).

Table 4.3 Relationship between hypertrophic PWS with color, location, and sublocation of the lesions

Factors	Hypertrophic PWS		P-value
	No, n(%)	Yes, n(%)	
Color of the lesion			
Pink	4 (3.7)	0 (0)	0.583[f]
Red	76 (70.4)	10 (37.0)	0.001[c]
Purple	28 (25.9)	17 (63.0)	0.003[c]
Lesion surface			0.780[c]
<50% of each location	75 (69.4)	18 (66.7)	
<50% of each location	33 (30.6)	9 (33.3)	
Face			
V1	26 (24.1)	7 (25.9)	0.841[c]
V2	31 (28.7)	12 (44.4)	0.116[c]
V3	15 (13.9)	10 (37.0)	0.006[c]
Upper eyelid	17 (15.7)	7 (25.9)	0.260[c]
Lower eyelid	8 (7.4)	3 (11.1)	0.460[c]
Upper lip	12 (11.1)	10 (37.0)	0.003[c]
Lower lip	2 (1.9)	4 (14.8)	0.015[c]
Oral mucosa	0 (0)	6 (22.2)	< 0.001[c]
Scalp	10 (9.3)	0 (0)	0.211[f]
Temporal	4 (3.7)	0(0)	0.583[f]
Occipital	6 (5.6)	0 (0)	0.599[f]
Neck	19 (17.6)	4 (14.8)	1.00[f]
Anterior	5 (4.6)	0 (0)	0.583[f]

Table 4.3 Relationship between hypertrophic PWS with color, location, and sublocation of the lesions (Cont.)

Factors	Hypertrophic PWS	P-value

	No, n(%)	Yes, n(%)	
Lateral	14 (13.0)	4 (14.8)	0.758[f]
Trunk	12 (11.1)	3 (11.1)	1.00[f]
Anterior	10 (9.3)	2 (7.4)	1.00[f]
Posterior	2 (1.9)	0 (0)	1.00[f]
Midline	2 (1.9)	2 (7.4)	0.178[f]
Lateral	10 (9.3)	1 (3.7)	0.693[f]
Arm	13 (12.0)	2 (7.4)	0.735[f]
Proximal	7 (6.5)	1 (3.7)	1.00[f]
Distal	8 (7.4)	1 (3.7)	0.687[f]
Forearm	10 (9.3)	1 (3.7)	0.693[f]
Proximal	6 (5.6)	0 (0)	0.599[f]
Distal	8 (7.4)	1 (3.7)	0.687[f]
Thigh	4 (3.7)	0 (0)	0.583[f]
Proximal	3 (2.8)	0 (0)	1.00[f]
Distal	1 (0.9)	0 (0)	1.00[f]
Leg	9 (8.3)	2 (7.4)	1.00[f]
Proximal	5 (4.6)	1 (3.7)	1.00[f]
Distal	7 (6.5)	1 (3.7)	1.00[f]
Hand	3 (2.8)	0 (0)	1.00[f]
Dorsal	2 (1.9)	0 (0)	1.00[f]
Ventral	1 (0.9)	0 (0)	1.00[f]
Foot	1 (0.9)	1 (3.7)	0.361[f]
Dorsal	1 (0.9)	1 (3.7)	0.361[f]
Ventral	1 (0.9)	0 (0)	1.00[f]

Statistical method used: f = Fisher's exact test, c = Chi-square test.

4.3 The relationship between Complication (bleeding, ulcer, pyogenic granuloma) with Location and sublocation

From the table 4.4, it was found that the relationship between complications (such as bleeding, ulcer, and pyogenic granuloma) and all locations and sublocations including face, scalp, neck, trunk, arm, forearm, thigh, legs, hands and foot did not show statistical differences.

Table 4.4 Relationship between Complication (bleeding, ulcer, pyogenic granuloma) with Location and sublocation

Factors	Complication (bleeding, ulcer, pyogenic granuloma)		P-value[f]
	No (n=126)	Yes (n=9)	
Face			
V1	31 (24.6)	2 (22.2)	1.00
V2	41 (32.5)	2 (22.2)	0.718
V3	22 (17.5)	3 (33.3)	0.367
Upper eyelid	22 (17.5)	2 (22.2)	0.661
Lower eyelid	10 (7.9)	1 (11.1)	0.546
Upper lip	21 (16.7)	1 (11.1)	1.00
Lower lip	5 (4.0)	1 (11.1)	0.344
Oral mucosa	5 (4.0)	1 (11.1)	0.344
Scalp	8 (6.3)	2 (22.2)	0.134
Temporal	3 (2.4)	1 (11.1)	0.244
Occipital	5 (4.0)	1 (11.1)	0.344
Neck	22 (17.5)	1 (11.1)	1.00
Anterior	5 (4.0)	0 (0)	1.00
Lateral	17 (13.5)	1 (11.1)	1.00

Table 4.4 Relationship between Complication (bleeding, ulcer, pyogenic granuloma) with Location and sublocation (Cont.)

Factors	Complication (bleeding, ulcer, pyogenic granuloma)		P-value[f]
	No (n=126)	Yes (n=9)	
Trunk	14 (11.1)	1 (11.1)	1.00
Anterior	11 (8.7)	1 (11.1)	0.579
Posterior	2 (1.6)	0 (0)	1.00
Midline	3 (2.4)	1 (11.1)	0.244
Lateral	11 (8.7)	0 (0)	1.00
Arm	15 (11.9)	0 (0)	0.597
Proximal	8 (6.3)	0 (0)	1.00
Distal	9 (7.1)	0 (0)	1.00
Forearm	11 (8.7)	0 (0)	1.00
Proximal	6 (4.8)	0 (0)	1.00
Distal	9 (7.1)	0 (0)	1.00
Thigh	4 (3.2)	0 (0)	1.00
Proximal	3 (2.4)	0 (0)	1.00
Distal	1 (0.8)	0 (0)	1.00
Leg	9 (7.1)	2 (22.2)	0.159
Proximal	5 (4.0)	1 (11.1)	0.344
Distal	7 (5.6)	1 (11.1)	0.433
Hand	3 (2.4)	0 (0)	1.00
Dorsal	2 (1.6)	0 (0)	1.00
Ventral	1 (0.8)	0 (0)	1.00
Foot	2 (1.6)	0 (0)	1.00
Dorsal	2 (1.6)	0 (0)	1.00
Ventral	1 (0.8)	0 (0)	1.00

4.4 The relationship between locations or sublocation and the anomalies in PWS patients

Considering specific anomalies among 135 PWS patients, anomalies or syndromes were identified in 2.2% of the patients, with eye-related issues (glaucoma, visual loss) accounting for 1.5%. Sturge-Weber syndrome (SWS),0.7% was the only syndrome identified in this study, as depicted in Table 4.5. The relationship between locations or sublocations and anomalies or SWS in PWS patients is detailed in Table 4.6. The relationship between all locations or sublocations and the anomalies or SWS in PWS patients was not significantly associated.

Table 4.5 Number and percent of associated anomalies among 135 PWS patients

Abnormalities or syndrome	Number	%	PWS locations
Eye	2	1.5	
Glaucoma	1	0.7	V1, V2
Visual Loss	1	0.7	V1, V2
Sturge-Weber syndrome	1	0.7	V1, V2

Table 4.6 Relationship between locations or sublocations and the anomalies or SWS in PWS patients

Factors	Abnormality		P-value[f]
	No (n=132)	Yes (n=3)	
Lesion surface			0.228
<50% of each location	92 (69.7)	1 (33.3)	
>50% of each location	40 (30.3)	2 (66.7)	
Face			
V1	31 (23.5)	2 (66.7)	0.148

Table 4.6 Relationship between locations or sublocations and the anomalies or SWS in PWS patients (Cont.)

Factors	Abnormality		P-value[f]
	No (n=132)	Yes (n=3)	
V2	41 (31.1)	2 (66.7)	0.238
V3	24 (18.2)	1 (33.3)	0.462
Sublocation			
Upper eyelid	23 (17.4)	1 (33.3)	0.447
Lower eyelid	10 (7.6)	1 (33.3)	0.227
Upper lip	20 (15.2)	2 (66.7)	0.069
Lower lip	6 (4.5)	0 (0)	1.00
Oral mucosa	6 (4.5)	0 (0)	1.00
Scalp	10 (7.6)	0 (0)	1.00
Temporal	4 (3.0)	0 (0)	1.00
Occipital	6 (4.5)	0 (0)	1.00

Statistical method used: f = Fisher's exact test

4.5 The relationship between locations or sublocation and the anomalies in PWS patients related to Face only

Analyzing into specific anomalies among 79 cases for Face only in PWS patients, anomalies or syndromes were identified in 3.8% of the patients, with eye-related issues (glaucoma, visual loss) accounting for 1.3%. Sturge-Weber syndrome (SWS) was the only syndrome identified in this study, as depicted in Table 4.7 The relationship between locations or sublocations and anomalies or SWS in PWS patients is detailed in Table 4.8 The relationship between all locations or sublocations and the anomalies or SWS in PWS patients was not significantly associated.

Table 4.7 Number and percent of associated anomalies among 79 cases for Face only in PWS patients

Abnormalities or syndrome	Number	%	PWS locations
Eye	2	2.5	
Glaucoma	1	1.3	V1, V2
Visual Loss	1	1.3	V1, V2
Sturge-Weber syndrome	1	1.3	V1, V2

Table 4.8 Relationship between locations or sublocations and the anomalies or SWS in PWS patients (79 cases for Face only)

Factors	Abnormality		P-value[f]
	No (n=132)	Yes (n=3)	
Lesion surface			0.285
<50% of each location	50 (65.8)	1 (33.3)	
>50% of each location	26 (34.2)	2 (66.7)	
Face			
V1	31 (40.8)	2 (66.7)	0.568
V2	41 (53.9)	2 (66.7)	1.00
V3	24 (31.6)	1 (33.3)	1.00
Sublocation			
Upper eyelid	22 (28.9)	1 (33.3)	1.00
Lower eyelid	9 (11.8)	1 (33.3)	0.337
Upper lip	19 (25.0)	2 (66.7)	0.171
Lower lip	6 (7.9)	0 (0)	1.00
Oral mucosa	6 (7.9)	0 (0)	1.00
Scalp	4 (5.3)	0 (0)	1.00
Temporal	4 (5.3)	0 (0)	1.00

Table 4.8 Relationship between locations or sublocations and the anomalies or SWS in PWS patients (79 cases for Face only) (Cont.)

Factors	Abnormality		P-value[f]
	No (n=132)	Yes (n=3)	
Occipital	0 (0)	0 (0)	cannot compute

Statistical method used: [f] = Fisher's exact test

4.6 The relationship between hypertrophic PWS with color, location, and sublocation of the lesions among PWS patients related to face only

Among 79 cases of PWS patients with facial involvement, it was found that V3, upper lip, lower lip and oral mucosa sublocations were significantly related to hypertrophic PWS (p-values 0.041, 0.006, 0.033 and < 0.001, respectively) as shown in Table 4.9.

Table 4.9 Relationship between hypertrophic PWS with color, location, and sublocation of the lesions among PWS patients related to face only

Factors	Hypertrophic PWS		P-value
	No, n(%)	Yes, n(%)	
Color of the lesion			
Pink	2 (3.4)	0 (0)	1.00[f]
Red	39 (66.1)	10 (50.0)	0.200[c]
Purple	18 (30.5)	10 (50.0)	0.115[c]
Lesion surface			0.622[c]
<50% of each location	39 (66.1)	12 (60.0)	
>50% of each location	20 (33.9)	8 (40.0)	
Face			

Table 4.9 Relationship between hypertrophic PWS with color, location, and sublocation of the lesions among PWS patients related to face only (Cont.)

Factors	Hypertrophic PWS		P-value
	No, n(%)	Yes, n(%)	
V1	26 (44.1)	7 (35.0)	0.477[c]
V2	31 (52.5)	12 (60.0)	0.563[c]
V3	15 (25.4)	10 (50.0)	0.041[c]
Upper eyelid	16 (27.1)	7 (35.0)	0.503[c]
Lower eyelid	7 (11.9)	3 (15.0)	0.708[f]
Upper lip	11 (18.6)	10 (50.0)	0.006[c]
Lower lip	2 (3.4)	4 (20.0)	0.033[f]
Oral mucosa	0 (0)	6 (30.0)	< 0.001[f]

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

As is well known, PWS undergoes changes over time due to the progression of dilated vessels in the papillary and upper reticular dermis. The proposed pathogenesis of PWS includes neuronal dysregulation, genetic alterations (GNAQ gene), and overexpression of vascular endothelial growth factors (VEGF). Lesions may shift in color from pink or red to deep red or purple, and hypertrophy or nodularity may develop, especially in untreated lesions (Barsky, Rosen, Geer, & Noe, 1980; Enzinger & Weiss, 1988). Dynamic changes in lesions and the limitations of laser treatment lead to resistant and recalcitrant PWS due to heterogeneity, as well as deeper, excessively small, or excessively large dilated vessels, and the formation of fibrous tissue (Finley, Noe, Arndt, & Rosen, 1984; Jamjanya, Vejjabhinanta, Tanasombatkul, & Phinyo, 2023). This study analyzed PWS patients across various age groups, including information on advanced lesions, especially hypertrophy, nodules, and complications of the disease. Furthermore, the setting included complicated conditions such as large lesions (more than 50% of each location) and associated anomalies or syndromes. The face was the most commonly affected location, consistent with other articles reporting higher cosmetic concerns in this area, especially among female patients. This study found hypertrophy and nodules at 20% and 10.4%, respectively. The majority of the hypertrophic and nodular lesions were found at highest proportion at age range of 11-20 and 31-40 years, respectively, which seem to triggered to younger age group compared to some articles. According to Klapman et al., the peak age onset of thickening is 20 to 39 years (Klapman & Yao, 2001). Drooge et al.

also reported a median age of hypertrophy at 12 years and nodularity at 39 years, which is similar to our study. Although reported age-dependent hypertrophy may differ among various studies due to differences in PWS populations, previous treatments, and other study methodologies, similar results of red and purple PWS increasing the proportion of hypertrophy were found in most studies (Lee et al., 2015; van Drooge et al., 2012). Moreover, this retrospective study showed that the V3, upper lip, lower lip, and oral mucosa sublocations exhibited a significant difference in hypertrophic PWS, consistent with similar results from Drooge et al. and Lee et al., who reported the most common location of hypertrophy mostly occurred on the face, rarely occurring on extremities. After, we did further analysis into PWS patients related to face only, V3, upper lip, lower lip and oral mucosa sublocations were still significantly related to hypertrophic PWS.

Anomalies or syndromes were identified in a small percentage of patients, with eye and brain anomalies, including SWS predominantly found in the V1 and V2 sublocations. According to the consensus statement, the best predictor for SWS risks is facial PWS involving any part of the forehead, including the upper eyelid and the midline frontonasal prominence, which follows the embryonal vasculature, akin to the V1 distribution. However, we did not find any significantly associated between all locations or sublocations and the anomalies or SWS in PWS patients in our study. PWS patients with SWS related, might develop having glaucoma due to the formation of abnormal blood vessel , which may lead to increased intra-ocular pressure, that might cause severe visual impairment or loss, without treatment. When a face PWS is identified as at-risk, especially when it involves the forehead, eyes screening for glaucoma and neurology should be done. Referral to a specialist should be considered. (Sabeti et al., 2021). Advanced lesions, characterized by progressive vascular ectasia, hypertrophy, and nodularity, are prone to complications such as bleeding, ulcers, and pyogenic granulomas, as indicated by the results herein. Less commonly found complications include eczematous changes or infections, which were not found in this report (Higueros et al., 2017).

The major strengths of this study included the variable age and the analysis of advanced lesions in PWS patients. Moreover, this study had also included more details in location and sublocation, specific anomalies of PWS, and its complications, compared to some others articles. However, several limitations need to be addressed. First, there may be selection bias due to data being obtained from a tertiary medical center and a population seeking treatment, particularly among female patients. Therefore, caution must be exercised in generalizing the results. Additionally, some patients were excluded due to insufficient data for analysis. Second, there may be inaccurate data due to recall bias, such as the onset of the disease. However, this retrospective study is a crucial tool for comprehending the rare and prolonged natural history of PWS. Gaining more insight into the natural course of PWS will contribute to determining appropriate guidelines for management and preventive measures, particularly in advanced lesions like hypertrophy. Further large or multicenter studies and enhanced technologies, especially advanced photographic tools, will provide more valuable data for future research.

5.2 Recommendations

The complexity of the natural history of PWS is crucial for enhancing the management of individual patients. Understanding the associations between the characteristics of the lesions and their locations could contribute to more targeted interventions and a better comprehension of the natural history of PWS. Further advancement in research is necessary to explore more valuable data.

References

Arisa E., Ortiz, & Nelson Js. (2012). Port-wine stain laser treatments and novel approaches. *Facial Plastic Surgery : FPS,* 28(6). doi.org/10.1055/s-0032-1329936

Asahina, A., Watanabe, T., Kishi, A., Hattori, N., Shirai, A., Kagami, S., … Ohara, K. (2006). Evaluation of the treatment of port-wine stains with the 595-nm long pulsed dye laser: *A large prospective study in adult Japanese patients. Journal of the American Academy of Dermatology,* 54(3), 487–493. doi.org/10.1016/j.jaad.2005.11.1034

Augustin, M., Zschocke, I., Wiek, K., Peschen, M., & Vanscheidt, W. (1998). Psychosocial Stress of Patients with Port Wine Stains and Expectations of Dye Laser Treatment. *Dermatology,* 197(4), 353–360. doi.org/10.1159/000018031

Barsky, S. H., Rosen, S., Geer, D. E., & Noe, J. M. (1980). The Nature and Evolution of Port Wine Stains: *A Computer-assisted Study. Journal of Investigative Dermatology,* 74(3), 154–157. doi.org/10.1111/1523-1747.ep12535052

Brightman, L. A., Geronemus, R. G., & Reddy, K. K. (2015). Laser treatment of port-wine stains. *Clinical, Cosmetic and Investigational Dermatology,* 8, 27–33. doi.org/10.2147/CCID.S53118

Cao, K. P., Quang, M. N., Dinh, Q. N., Quynh, H. P., Hong, S. N., Van, T. N., … Lotti, T. (2019). Anatomical Evaluation for Successful Dye Laser Treatment of Port Wine Stain in Vietnamese Patients. *Open Access Macedonian Journal of Medical Sciences,* 7(2), 208–210. doi.org/10.3889/oamjms.2019.052

Chang, H. S., Kim, Y.-G., & Lee, J. H. (2011). Treatment Using a Long-Pulsed Nd:Yag Laser with a Pulsed Dye Laser for Four Cases of Blebbed Port Wine Stains. *Annals of Dermatology, 23(Suppl 1),* S75–S78. doi.org/10.5021/ad.2011.23.S1.S75

References (Cont.)

Chapas, A. M., Eickhorst, K., & Geronemus, R. G. (2007). Efficacy of early treatment of facial port wine stains in newborns: A review of 49 cases: TREATMENT OF FACIAL PORT WINE STAINS IN NEWBORNS. *Lasers in Surgery and Medicine,* 39(7), 563–568. doi.org/10.1002/lsm.20529

Diociaiuti, A., Paolantonio, G., Zama, M., Alaggio, R., Carnevale, C., Conforti, A., … El Hachem, M. (2021). Vascular Birthmarks as a Clue for Complex and Syndromic Vascular Anomalies. *Frontiers in Pediatrics,* 9. www.frontiersin.org/articles/10.3389/fped.2021.730393

Drooge, A. M. van, Beek, J. F., Veen, J. P. W. van der, Horst, C. M. A. M. van der, & Wolkerstorfer, A. (2012). Hypertrophy in port-wine stains: Prevalence and patient characteristics in a large patient cohort. *Journal of the American Academy of Dermatology,* 67(6), 1214–1219. doi.org/10.1016/j.jaad.2012.05.027

Elias, A. J., Hand, J. L., Tollefson, M. M., & Davis, D. M. R. (2021). The anatomic distribution of isolated and syndrome-associated port-wine stain. *Pediatric Dermatology,* 38(1), 77–82. doi.org/10.1111/pde.14392

Enjolras, O., Riche, M. C., & Merland, J. J. (1985). Facial port-wine stains and Sturge-Weber syndrome. *Pediatrics,* 76(1), 48–51.

Enzinger, F. M., & Weiss, S. W. (1988). *Soft tissue tumors (2nd Edition).* 521-522

Faurschou, A., Olesen, A. B., Leonardi-Bee, J., & Haedersdal, M. (2011). Lasers or light sources for treating port-wine stains. *Cochrane Database of Systematic Reviews,* 11. doi.org/10.1002/14651858.CD007152.pub2

Fernández-Guarino, M., Boixeda, P., de las Heras, E., Aboin, S., García-Millán, C., & Olasolo, P. J. (2008). Phakomatosis pigmentovascularis: Clinical findings in 15 patients and review of the literature. *Journal of the American Academy of Dermatology,* 58(1), 88–93. doi.org/10.1016/j.jaad.2007.08.012

References (Cont.)

Finley, J. L., Noe, J. M., Arndt, K. A., & Rosen, S. (1984). Port-wine stains. Morphologic variations and developmental lesions. *Archives of Dermatology,* 120(11), 1453–1455. doi.org/10.1001/archderm.120.11.1453

Gemert, M. J. C. van, Nelson, J. S., Milner, T. E., Smithies, D. J., Verkruysse, W., Boer, J., … Svaasand, L. O. (1997). Non-invasive determination of port wine stain anatomy and physiology for optimal laser treatment strategies. *Physics in Medicine and Biology,* 42(5), 937–950. doi.org/10.1088/0031-9155/42/5/013

Grazzini, M., Stanganelli, I., Rossari, S., Gori, A., Oranges, T., Longo, A. S., … De Giorgi, V. (2012). Dermoscopy, confocal laser microscopy, and hi-tech evaluation of vascular skin lesions: Diagnostic and therapeutic perspectives: Vascular skin lesions. *Dermatologic Therapy,* 25(4), 297–303. doi.org/10.1111/j.1529-8019.2012.01547.x

Haliasos, E. C., Kerner, M., Jaimes, N., Zalaudek, I., Malvehy, J., Lanschuetzer, C. M., … Marghoob, A. A. (2013). Dermoscopy for the Pediatric Dermatologist, Part II: Dermoscopy of Genetic Syndromes with Cutaneous Manifestations and Pediatric *Vascular Lesions. Pediatric Dermatology,* 30(2), 172–181. doi.org/10.1111/j.1525-1470.2012.01874.x

Han, Y., Ying, H., Zhang, X., Yu, W., Cen, Q., Chen, X., … Lin, X. (2020). Retrospective study of photodynamic therapy for pulsed dye laser-resistant port-wine stains. *The Journal of Dermatology,* 47(4), 348–355. doi.org/10.1111/1346-8138.15238

Higueros, E., Roe, E., Granell, E., & Baselga, E. (2017). Sturge-Weber Syndrome: A Review. *Actas Dermo-Sifiliográficas* (English Edition), 108(5), 407–417. doi.org/10.1016/j.adengl.2017.03.034

Ho, W. S., Chan, H. H., Ying, S. Y., & Chan, P. C. (2002). Laser treatment of congenital facial port-wine stains: Long-term efficacy and complication in Chinese patients. *Lasers in Surgery and Medicine,* 30(1), 44–47. doi.org/10.1002/lsm.10003

References (Cont.)

Hsiao, Y.-C., & Chang, C.-J. (2011). Update on flashlamp pumped pulsed dye laser treatment for port wine stains (capillary malformation) patients. *Laser Therapy,* 20(4), 265–272. doi.org/10.5978/islsm.11-RE-01

Jamjanya, S., Vejjabhinanta, V., Tanasombatkul, K., & Phinyo, P. (2023). Comparative effectiveness among available treatments in difficult-to-treat port-wine stains (PWS): A Network Meta-Analysis of observational evidence. *The Journal of Dermatological Treatment,* 34(1), 2231582. doi.org/10.1080/09546634.2023.2231582

Jasim, Z. F., & Handley, J. M. (2007). Treatment of pulsed dye laser–resistant port wine stain birthmarks. *Journal of the American Academy of Dermatology,* 57(4), 677–682. doi.org/10.1016/j.jaad.2007.01.019

Jean L., B., Julie V., S., & Lorenzo, C. (2018). *Bolognia Fourth Edition, dermatology* (4th ed., Vol. 2).

Kang, S., Amagai, M., Bruckner, A. L., Margolis, D. J., McMichael, A. J., & Orringer, J. S. (n.d.). *Fitzpatrick's Dermatology 9th Edition* (9th ed.).

Kelly, K. M., Choi, B., McFarlane, S., Motosue, A., Jung, B., Khan, M. H., …Nelson, J. S. (2005). Description and analysis of treatments for port-wine stain birthmarks. *Archives of Facial Plastic Surgery,* 7(5), 287–294. doi.org/10.1001/archfaci.7.5.287

Klapman, M. H., & Yao, J. F. (2001). Thickening and nodules in port-wine stains. *Journal of the American Academy of Dermatology,* 44(2), 300–302. doi.org/10.1067/mjd.2001.111353

Lam, S. M., & Williams, E. F. (2004). Practical Considerations in the Treatment of Capillary Vascular Malformations, or Port Wine. *Facial Plast Surg,* 20(1):71-6. doi: 10.1055/s-2004-822962. PMID: 15034817.

References (Cont.)

Lambiase, A., Mantelli, F., Bruscolini, A., La Cava, M., & Abdolrahimzadeh, S. (2016). Ocular manifestations of Sturge–Weber syndrome: Pathogenesis, diagnosis, and management. *Clinical Ophthalmology,* 871. doi.org/10.2147/OPTH.S101963

Lee, J. W., & Chung, H. Y. (2018). Capillary Malformations (Portwine Stains) of the Head and Neck. *Otolaryngologic Clinics of North America,* 51(1), 197–211. doi.org/10.1016/j.otc.2017.09.004

Lee, J. W., Chung, H. Y., Cerrati, E. W., O, T. M., & Waner, M. (2015). The Natural History of Soft Tissue Hypertrophy, Bony Hypertrophy, and Nodule Formation in Patients With Untreated Head and Neck Capillary Malformations. *Dermatologic Surgery,* 41(11), 1241–1245. doi.org/10.1097/DSS.0000000000000525

McCuaig, C. C. (2017). Update on classification and diagnosis of vascular malformations. *Current Opinion in Pediatrics,* 29(4), 448–454. doi.org/10.1097/MOP.0000000000000518

Minkis, K., Geronemus, R. G., & Hale, E. K. (2009). Port Wine Stain Progression: A Potential Consequence of Delayed and Inadequate Treatment? *Lasers in Surgery and Medicine,* 41(6), 423–426. doi.org/10.1002/lsm.20788

Morelli, J. G. (1995). Initial Lesion Size as a Predictive Factor in Determining the Response of Port-wine Stains in Children Treated With the Pulsed Dye Laser. *Archives of Pediatrics & Adolescent Medicine,* 149(10), 1142. doi.org/10.1001/archpedi.1995.02170230096014

Nguyen, Yohn, Huff, Weston, & Morelli. (1998). Facial port wine stains in childhood: Prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. *British Journal of Dermatology,* 138(5), 821–825. doi.org/10.1046/j.1365-2133.1998.02219.x

References (Cont.)

Ortiz, A., & Nelson, J. (2012). Port-Wine Stain Laser Treatments and Novel Approaches. *Facial Plastic Surgery,* 28(06), 611–620. doi.org/10.1055/s-0032-1329936

P Redondo. (2007). Vascular Malformations (I). Concept, Classification, Pathogenesis and Clinical Features. *Actas Dermo-Sifiliográficas* (English Edition), 98(3), 141–158. doi.org/10.1016/S1578-2190(07)70418-3

Passeron, T., Salhi, A., Mazer, J.-M., Lavogiez, C., Mazereeuw-Hautier, J., Galliot, C., …Lacour, J.-P. (2016). Prognosis and response to laser treatment of early-onset hypertrophic port-wine stains (PWS). *Journal of the American Academy of Dermatology,* 75(1), 64–68. doi.org/10.1016/j.jaad.2016.02.1167

Piccolo, V., Russo, T., Moscarella, E., Brancaccio, G., Alfano, R., & Argenziano, G. (2018). Dermatoscopy of Vascular Lesions. *Dermatologic Clinics,* 36(4), 389–395. doi.org/10.1016/j.det.2018.05.006

Prather, H. B., & Arndt, K. A. (2015). The Development of Hypertrophy in Port-Wine Stains, a Common Phenomenon that Affects Treatment Recommendations. *Dermatologic Surgery,* 41(11), 1246–1248. doi.org/10.1097/DSS.0000000000000524

Raath, M. I. van, Chohan, S., Wolkerstorfer, A., Horst, C. M. A. M. van der, Limpens, J., Huang, X., …Heger, M. (2020). Clinical outcome measures and scoring systems used in prospective studies of port wine stains: A systematic review. *PLOS ONE,* 15(7), e0235657. doi.org/10.1371/journal.pone.0235657

Rao, A., Reddy, Vs., Parimala, Md., Tejal, M., Fathima, K., Preeti, S., … Shruthi, T. (2020). Sturge–Weber syndrome coexisting with multiple vertebral vascular malformations and hemivertebra with scoliosis and upper limb and ear hypertrophy. *Indian Journal of Dermatology, Venereology and Leprology,* 86. doi.org/10.4103/ijdvl.IJDVL_445_19

References (Cont.)

Rozas-Muñoz, E., Frieden, I. J., Roé, E., Puig, L., & Baselga, E. (2016). Vascular Stains: Proposal for a Clinical Classification to Improve Diagnosis and Management. *Pediatric Dermatology,* 33(6), 570–584. doi.org/10.1111/pde.12939

Sabeti, S., Ball, K. L., Burkhart, C., Eichenfield, L., Faith, E. F., Frieden, I. J., …Kelly, K. M. (2021). Consensus Statement for the Management and Treatment of Port-Wine Birthmarks in Sturge-Weber syndrome. *JAMA Dermatology,* 157(1), 98–104. doi.org/10.1001/jamadermatol.2020.4226

Savas, J. A., Ledon, J. A., Franca, K., Chacon, A., & Nouri, K. (2013). Pulsed dye laser-resistant port-wine stains: Mechanisms of resistance and implications for treatment: Pulsed dye laser-resistant port-wine stains. *British Journal of Dermatology,* 168(5), 941–953. doi.org/10.1111/bjd.12204

Shi, W., Wang, J., Lin, Y., Geng, J., Wang, H., Gong, Y., … Zhang, F. (2014). Treatment of port wine stains with pulsed dye laser: A retrospective study of 848 cases in Shandong Province, People's Republic of China. *Drug Design, Development and Therapy,* 8, 2531–2538. doi.org/10.2147/DDDT.S71710

Siegel, D. H., Cottrell, C. E., Streicher, J. L., Schilter, K. F., Basel, D. G., Baselga, E., … Drolet, B. A. (2018). Analyzing the Genetic Spectrum of Vascular Anomalies with Overgrowth via Cancer Genomics. *Journal of Investigative Dermatology,* 138(4), 957–967. doi.org/10.1016/j.jid.2017.10.033

Slaughter, K. A., Chen, T., & Williams, E. (2016). Vascular Lesions. *Facial Plastic Surgery Clinics of North America,* 24(4), 559–571. doi.org/10.1016/j.fsc.2016.06.009

Tark, K. C., Lew, D. H., & Lee, D. W. (2011). The fate of long-standing port-wine stain and its surgical management. *Plastic and Reconstructive Surgery,* 127(2), 784–791. doi.org/10.1097/PRS.0b013e318200a9e7

References (Cont.)

Tran, J. M., Kelly, K. M., Drolet, B. A., Krakowski, A. C., & Arkin, L. M. (2021). Light-based treatment of pediatric port-wine birthmarks. *Pediatric Dermatology,* 38(2), 351–358. doi.org/10.1111/pde.14503

van Drooge, A. M., Beek, J. F., van der Veen, J. P. W., van der Horst, C. M. A. M., & Wolkerstorfer, A. (2012). Hypertrophy in port-wine stains: Prevalence and patient characteristics in a large patient cohort. *Journal of the American Academy of Dermatology,* 67(6), 1214–1219. doi.org/10.1016/j.jaad.2012.05.027

van Raath, M. I., Chohan, S., Wolkerstorfer, A., van der Horst, C. M. a. M., Storm, G., & Heger, M. (2019). Port wine stain treatment outcomes have not improved over the past three decades. *Journal of the European Academy of Dermatology and Venereology: JEADV,* 33(7), 1369–1377. doi.org/10.1111/jdv.15599

van Raath, M. I., Chohan, S., Wolkerstorfer, A., van der Horst, C. M. A. M., Limpens, J., Huang, X., … Heger, M. (2021). Treatment Outcome Measurement Instruments for Port Wine Stains: A Systematic Review of Their Measurement Properties. *Dermatology,* 237(3), 416–432. doi.org/10.1159/000511438

Wanitphakdeedecha, R., Jantarakolica, T., Ng, J. N. C., Yan, C., Nanchaipruek, Y., Jantanapornchai, N., … Sudhipongpracha, T. (2021). The Cost-Effectiveness of Pulsed-Dye Laser Therapy Among Thai Patients with Facial Port-Wine Stain: A Retrospective Study and Economic Evaluation. *Dermatology and Therapy,* 11(2), 465–473. doi.org/10.1007/s13555-021-00484-1

Wanitphakdeedecha, R., Ng, J. N. C., Yan, C., Manuskiatti, W., Sudhipongpracha, T., & Jantarakolica, T. (2021). Quality of Life and Psychological Effects of Port-Wine Stain: A Review of Literature. *Clinical, Cosmetic and Investigational Dermatology,* 14, 681–690. doi.org/10.2147/CCID.S315804

References (Cont.)

Wassef, M., Blei, F., Adams, D., Alomari, A., Baselga, E., Berenstein, A., … Vikkula, M. (2015). Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics,* 136(1), e203–e214. doi.org/10.1542/peds.2014-3673

Yang, B., Yang, O., Guzman, J., Nguyen, P., Crouzet, C., Osann, K. E., … Choi, B. (2015). Intraoperative, Real-Time Monitoring of Blood Flow Dynamics Associated With Laser Surgery of Port Wine Stain Birthmarks. *Lasers in Surgery and Medicine,* 47(6), 469–475. doi.org/10.1002/lsm.22369

Zhang, X.-Y., Al-Odaini, N., Zheng, W.-J., Fan, R.-G., Xiong, H., Huang, J.-C., … Wen, S.-J. (2022). The Relationship Between the Effectiveness of HMME-PDT and the Dermoscopic Features of Port-wine Stains in Chinese Pediatric Patients: A Retrospective Study. *Dermatology and Therapy,* 12(7), 1671–1683. doi.org/10.1007/s13555-022-00757-3

Appendix

Case Record Form

Case No.....

Clinical manifestations analysis of Port wine stain patients at the Institute of Dermatology, Thailand, 5 years retrospective study.

1. Gender ◯ Male ◯ Female
2. Age: ..... years
3. Skin type: ◯ I ◯ II ◯ III ◯ IV ◯ V ◯ VI
4. Previous treatment (before attending IOD): ◯ Yes ◯ No

   If yes, ◯ laser specify.....

   ◯ other specify.....

   Number of treatments: ..... times
5. Clinical manifestations:

   5.1 Color of the lesion ◯ Pink ◯ Red ◯ Purple ◯ Hyperpigmentation ◯ Hypopigmentation

   5.2 Aspect of the lesions

   ◯ Homogeneous ◯ Heterogeneous

   ◯ Symmetry ◯ Asymmetry

   ◯ Flat ◯ Hypertrophic ◯ Atrophic ◯ Nodule ◯ Cobblestone

   ◯ Geographic ◯ Reticulated ◯ Multiple discrete

   5.3 Lesion onset: ..... years.

   5.4 Border of the lesion ◯ well-defined ◯ Ill-defined ◯ Peripheral halo

   5.5 Lesion surface (of each location): ◯ <50% ◯ >50%

   5.6 Location ◯ V1 ◯ V2 ◯ V3 ◯ Other dermatome distribution, specify.....

Left Right

Signature..... Date.....

Update 15-5-2023

◯ Upper eyelid ◯ Lower eyelid

◯ Upper lip ◯ Lower lip ◯ mucosa involvement

◯ Scalp ◯ Temporal ◯ Parietal ◯ Occipital
◯ Neck ◯ Anterior ◯ Posterior ◯ Lateral

◯ Trunk ◯ Anterior ◯ Posterior ◯ Midline ◯ Lateral

◯ Arm ◯ Proximal ◯ Distal ◯ Anterior ◯ Posterior

◯ Forearm ◯ Proximal ◯ Distal ◯ Anterior ◯ Posterior

◯ Thigh ◯ Proximal ◯ Distal ◯ Anterior ◯ Posterior

◯ Leg ◯ Proximal ◯ Distal ◯ Anterior ◯ Posterior

◯ Hand ◯ Dorsal ◯ Ventral

◯ Foot ◯ Dorsal ◯ Ventral

5.7 Complications ◯ No ◯ Bleeding ◯ Ulcer ◯ Pyogenic granuloma
◯ Other.....

6. Associated abnormalities or syndrome:

◯ None

◯ Eye ◯ Glaucoma ◯ Visual Loss ◯ Other.....

◯ Brain ◯ Epilepsy ◯ Mental retardation ◯ Macrocepahly ◯ Other.....

◯ Musculoskeletal ◯ Scoliosis ◯ Limb hypertrophy ◯ Other.....

◯ Sturge-Weber syn ◯ Klippel Trenaunay syn ◯ Parkes-Weber syn

◯ Phakomatosis pigmentovascularis ◯ PTEN hamartoma tumor syn

◯ Congenital lipomatous overgrowth, vascular malformations, epidermal nevus, spinal/skeletal anomalies/scoliosis syndrome (CLOVES)

◯ Diffuse capillary malformation with overgrowth (DCMO)

◯ Macrocephaly-capillary malformation (M-CM) ◯ Other.....

Signature..... Date.....

Biography

Name	Kettya Hong
Date of birth	01 February 1993
Place of birth	Siem Reap, Cambodia
Education background	University of Health Science Diploma of Doctor of Medicine, 2019
Address	G32, St. Gold, Tummob Tuek, Boeng Kengkang, Phnom Penh, Cambodia
Email Address	hongkettya7@gmail.com
Place of work	Khmer-Soviet Friendship Hospital
Work position	Dermatologist