A typical manifestationof Cutaneous Infantile Hemangiomas: A Case Series.

Abstract

Background: Infantile hemangioma, also called 'strawberry naevus' is the most prevalent benign vascular tumor in children, affect 4% to 10% of infants. Proliferation of endothelial cells cause these lesions in early infancy and a gradual involution over years. Treatment includes topical beta-blockers, oral corticosteroids& beta blockers, laser therapy, or surgical options in certain cases.In this case series, we have drawn comparison between typical and atypical presentations of IH in infants with emphasis on the possibility of finding atypical presentations and their timely management.

The aim of study: To assess changes in size, location, morphology, progression and treatment response in varieties of hemangioma.

Case Reports:We presented two casesof IH presented at NBH/HUH, Karachi. Case 1 involved a 3-month-old female with a typical presentation characterized by a solitary, asymmetric rapidly enlarging vascular lesion on right deltoid region, treated with 2% topical propranolol and oral steroids. Case 2 involved a 3-month-old male with an atypical presentation characterized by multiple,bilateral symmetrical lesions (very rare manifestation) on extensor surfaces of both wrists and the genital area treated with 2% propranolol.

Conclusion: Early Recognition of such uncommon manifestations is essential to avoid misdiagnosis, exclude other differentials, anticipate common complications and initiate timely treatment, particularly in high-risk anatomical sites to prevent morbidity and good treatment response.

Key Words: Hemangioma, strawberry naevus,infantile hemangioma, vascular tumor, vascular malformation, propranolol, superficial hemangioma.

Abbreviations:

IH = Infantile hemangioma
GLUT-1 = Glucose Transporter 1
VEGFR = Vascular Endothelial Growth Factor Receptors
VEGF-A = Vascular Endothelial Growth Factor A
IGF-2 = Insulin-like Growth Factor 2
HIF-1α = Hypoxia-inducible factor 1-alpha (HIF-1α)
bFGF = Basic fibroblast growth factor
CVS = Cardiovascular System
CNS = Central Nervous System

Nd:YAG = Neodymium-doped Yttrium Aluminum Garnet
MMP = Matrix Metalloproteinase
FDS = Flexor Digitorum Superficialis
FDP = Flexor Digitorum Profundus

Introduction

The most prevalent benign vascular tumors of infancy are infantile hemangiomas (IH), which usually manifest in the first few weeks of life and affect 4% to 10% in Caucasian infants, with some variation across populations. [1] IH is more common in female infants (female to male ratioof 1.4:1 to 3.1), twins, premature infants,Caucasians, low birth weight infants, multiple pregnancies, preeclampsia, placental anomalies, and positive family history of IH in a first-degree relative.

IHs are clinically characterized by a proliferative phase followed by regression phase, but 10% of cases require early treatment due to its location, size and complications otherwise spontaneous regression do not require any treatment. Clinical features of IH are not present at birth but develop in the first 1-2 weeks after birth, rapidly multiply within 1–3 months of age, stop proliferating until 5 months and then slowly regress into adipose and fibrous tissue until 4 years but up to the age of 10 years in some cases.

Pathologically, IHs are glucose transporter-1 protein (GLUT-1)positive, which distinguishes them from other vascular tumors but its pathogenesis has not been completely explained. There are several key hypotheses explaining IH. The first suggests that increased VEGFR signaling and mutations in hemangioma stem cells (derived from $CD34^{+}/CD133^{+}$ endothelial progenitor cells) promote differentiation into GLUT-1positive endothelial cells under angiogenic factors like VEGF-A and HIF-1α. The second, the placental embolization theory, proposes that displaced placental cells drive hemangioma formation, mimicking placental growth and regression. The third hypothesis links tissue hypoxia (e.g., prematurity, low birth weight) to HIF-1α–mediated angiogenesis via VEGF and bFGF. The fourth involves the renin–angiotensin system, where elevated renin and angiotensin activity stimulate proliferation, while Beta-blockers promote regression by inhibiting renin release. [2]

Infantile hemangiomas can be broadly categorized as localized, segmental, or multifocal lesions based on their distribution and morphological features, such as superficial, deep, and mixed types, or reticular/abortive/minimal growth types. [3]

Superficial IHs are located in the epidermis and dermis with little or no subcutaneous involvement, appearing bright red and previously termed “strawberry hemangiomas,” while deep IHs lie beneath the skin surface, are more diffuse and ill-defined, and present with normal skin color or a bluish hue, formerly called “cavernous hemangiomas.” Mixed IHs include both superficial and deep components, and deep or mixed types typically involve deeper soft tissues and become noticeable around 1–2 months of age or later. [2]

Although the majority of IH manifest as single, localized cutaneous lesions, bilateral or multifocal presentations are uncommon and are rarely reported in the literature, so it is crucial to record and examine such cases. IH can develop anywhere on the body, but they most commonly occur in the head and neck region (60%), followed by the trunk (25%) and the extremities (15%), reflecting their well-documented predilection for the head and neck area [4]Hemangiomaof the genitalia is extremely uncommon.Genital hemangioma is self-limited (resolves spontaneously), therefore conservative treatment is usuallysuggested. [5] The exact cause of glans hemangioma remains unclear; it is variously considered a benign vascular tumor or congenital vascular anomaly, while other theories suggest it may result from herniation of cavernosal tissue or develop secondary to a prior penile hematoma.

Treatment options for small hemangiomas include surgical excision, cryotherapy and electrofulguration.Recent treatment includes sclerotherapy and laser fulguration.Surgical excision of penile hemangioma has an increasedrisk of bleeding during the excision because of rich blood supply of penis but nocturnal erections may occur post-operatively. Laser treatment with Nd:YAG in hemangioma of glans penis has also been successfully suggested. [6]

The majority of lesions are asymptomatic and disappear on their own, but a small percentage can cause ulceration, bleeding, infection, associated structural anomalies, disfigurement anddepending on the anatomical location, functional impairment like airway or vision obstruction. [1]

Diagnosis of infantile hemangiomas is uncertain and needs differentiation from other vascular malformations. Imaging modalitiessuch as ultrasonography with Doppler, magnetic resonance angiography (MRA) or magnetic resonance imaging (MRI) may be useful for the diagnosis of IHand monitor their responseto treatment.

Regarding its treatment,timolol maleate, a topical nonselective beta-blocker, is used at a dose of 1–2 drops of 0.5% gel-forming ophthalmic solution, applied twice daily for the treatment of small, thin and superficial Hemangiomas.

Oral standard treatment strategies include corticosteroids and oral propranolol (non-selective beta-adrenergic antagonist). Oral propranolol is thegold standard treatment for high-risk IHs at a dosage of 2–3 mg/kg/day in 2 daily divided doses for atleast 6 months. [2]

Propranolol causes early color change in hemangiomas (pink to violaceous) due to vasoconstriction, reduces growth by downregulating proangiogenic factors (e.g., MMP-2, MMP-9, bFGF, VEGF), and promotes endothelial cell apoptosis, leading to lesion regression.Atenololis a selective beta-1antagonist whichcan also be used in a dose of 1 mg/kg/dayand has a decreased risk of bronchospasm and hypoglycemia.

Oral steroids were previously used for treatment of hemangiomas in a dose of 2–3 mg/kg/day for 9 to 12 months but their use was gradually reduced since beta blockers introduced.Combined treatment of propanol and corticosteroids can be used in complicated

cases of hemangiomas.Intra-lesional steroid injections can be helpful for small and initial proliferating stage of IHs. [7]
Pulse-dye laser therapy (PDL) or surgery is recommended for the treatment of residual skin changes after IH regression but may be used earlier to treat selected cases of IHs.[2]

The natural history and outcomes of IH highlight the significance of early detection: although many hemangiomas regress with passage of time,complex or high-risk lesions can cause serious morbidity or irreversible cosmetic changes if left untreated. [8]This case of bilateral infantile hemangioma advances knowledge of the clinical range of this prevalent pediatric vascular tumor because bilateral involvement is very uncommon and may have consequences for treatment and results.

Case Presentation

Case 1

A 3-month-old female infant presented to the skin outpatient department at Naimat Begum Hospital/Hamdard University Hospital Karachi, with a rapidly enlarginglesion over the right deltoid region. She was born at full term with a birth weight of 2.3 kg via spontaneous vaginal delivery. The lesion was first noted at approximately 1 month of age and showed progressive enlargement.Prenatal, natal, and post-natal history was not significant.Vaccination history was up-to-date.
On gross examination, the child looked healthy and comfortable. Skin examination showed an oval lesion,10×7 cm in size, erythematousin color, edematous, palpable boggy mass, presented on right upper deltoid region. (Figure 1A) It was soft, normothermic, non-tender and compressible, with no evidence of ulceration or spontaneous bleeding while rest of the skin,hairs and nails were normal.There was normal muscle structure and function and no muscle atrophy/dystrophy or joint deformity was noted in the right limb. Pulse was normal, sensation and joint reflexes were intact in the involved limb. No pressure symptoms were noted. Rest of the systemic examination like CVS, CNS, respiratory,abdominal, urogenital and locomotory was unremarkable.

The differential diagnoses considered included infantile fibrosarcoma, non-involuting congenital hemangioma (NICH), kaposiform hemangioendothelioma, tufted angioma, and pyogenic granuloma, all of which can present as vascular or soft-tissue lesions in infancy. However, the postnatal onset, rapid growth during early infancy, and classic clinical morphology favored a diagnosis of infantile hemangioma. No imaging studies were performed due to the typical clinical presentation and absence of red-flag features. Topical 2% propranolol therapy was initiated on the day of presentation. Subsequently, oral corticosteroids in a dose of 0.5 mg/kg body weight were added to enhance regression.

At follow-up visits till age of 1 year, marked regression in lesion size, thickness with few areas of atrophy, and color was observed. (Figure 1B) The treatment was well tolerated, with no adverse

events noted. Written informed parental consent was obtained, and serial clinical photographs documenting pre- and post-treatment changes (over one year of age) were recorded.

Case 2

A 3-month-old male infant presented 1st time to the skin OPD at Naimat Begum Hospital/Hamdard University Hospital Karachi,with bilateral symmetrical erythematous lesions involving both wrists and the genital region. According to mother,child was hospitalized just after birth due to chest congestion and the lesions have developed at the site of cannulization on both wrists.He was born full term with a birth weight of 2.8 kg. The lesions were first noticed at 2 months of age and progressively increased in size. There was no history of pain/difficulty in joint movement of both upper limbs or duringmicturition or defecation.Prenatal, natal, and post-natal history was not significant.Vaccination history is up-to-date.

On gross examination,the child looked healthy and comfortable. Skin examination showed there weremultiple well-demarcated, erythematous soft tissue swellings, present over both wrists and the genital/perineal area. (Figure 2) It was soft, normothermic, non-tender, and compressiblewhile rest of the skin,hairs and nails were normal.There was normal muscle structure and function and no muscle atrophy/dystrophy or joint deformity was noted in the both upper limbs and wrist. Pulse was normal, no radio-radial or radio-femoral delay, sensation and joint reflexes were intact in bothupper limbs and wrist. No pressure symptoms were noted. There was no ulceration, telangiectasia, significant bleeding, or associated anorectal or urogenital anomaly on clinical assessment. Rest of the systemic examination like CVS, CNS, respiratory, abdominal, urogenital and locomotory systemswere unremarkable.

Topical 2% propranolol and topical steroid were initiated on the day of presentation. The patient was advised regular follow-up for clinical monitoring but patient did not return for follow-up, and therefore treatment response and long-term outcomes could not be assessed. Written informed parental consent was obtained at initial presentation, and clinical photographs were taken for documentation.

Characteristics	Case 1	Case 2
Age at presentation	3 months	3 months
Sex	Female	Male
Birth weight	2.3 kg	2.8 kg
Lesion site	Deltoid region	Bilateral wrists + genital

		region
Lesion size	Single (10 × 7 cm)	Multiple superficial
Differential diagnosis	Ruled out clinically	IH diagnosed clinically
Treatment	Topical 2% propranolol Topical steroid Oral steroids	Topical 2% propranolol Topical steroid
Outcome	Regression observed	Lost to follow-up

Table 1: summary table of case 1 and case 2

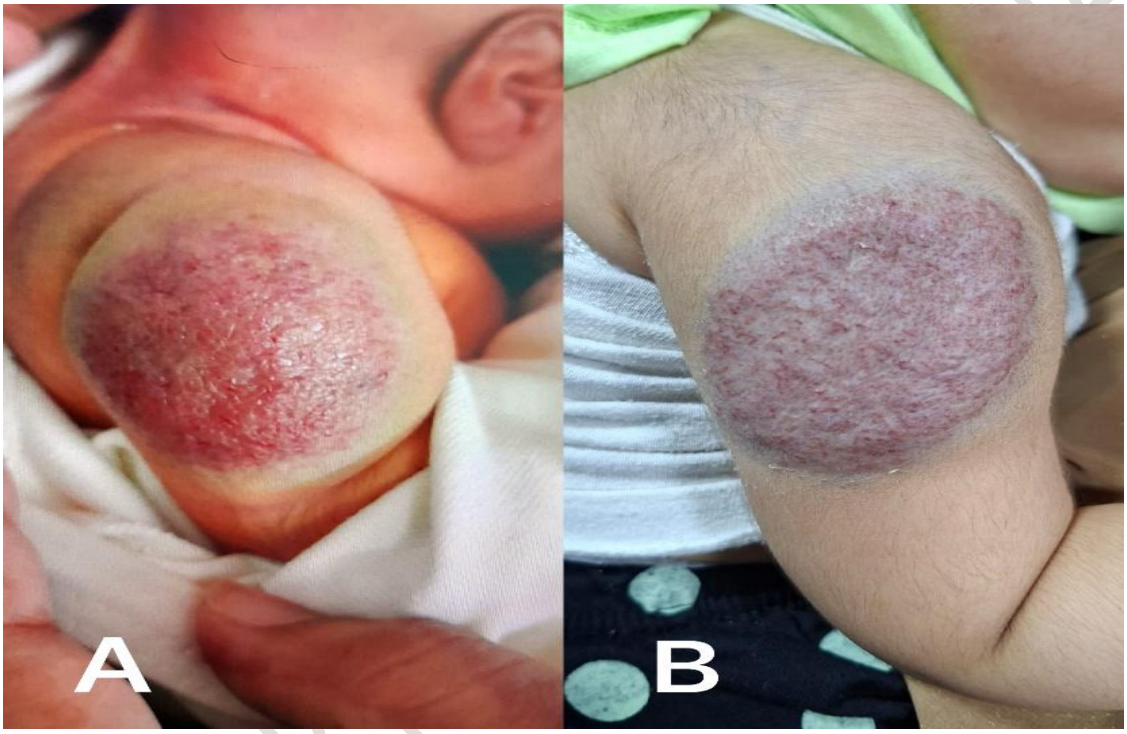

Figure 1: Case 1 (A) oval lesion, 10 × 7 cm in size, erythematous in color, edematous, palpable boggy mass, presented on right upper deltoid region (B) change in color from erythematous to violaceous with few areas of atrophy and decrease in thickness of the lesion on follow-up.

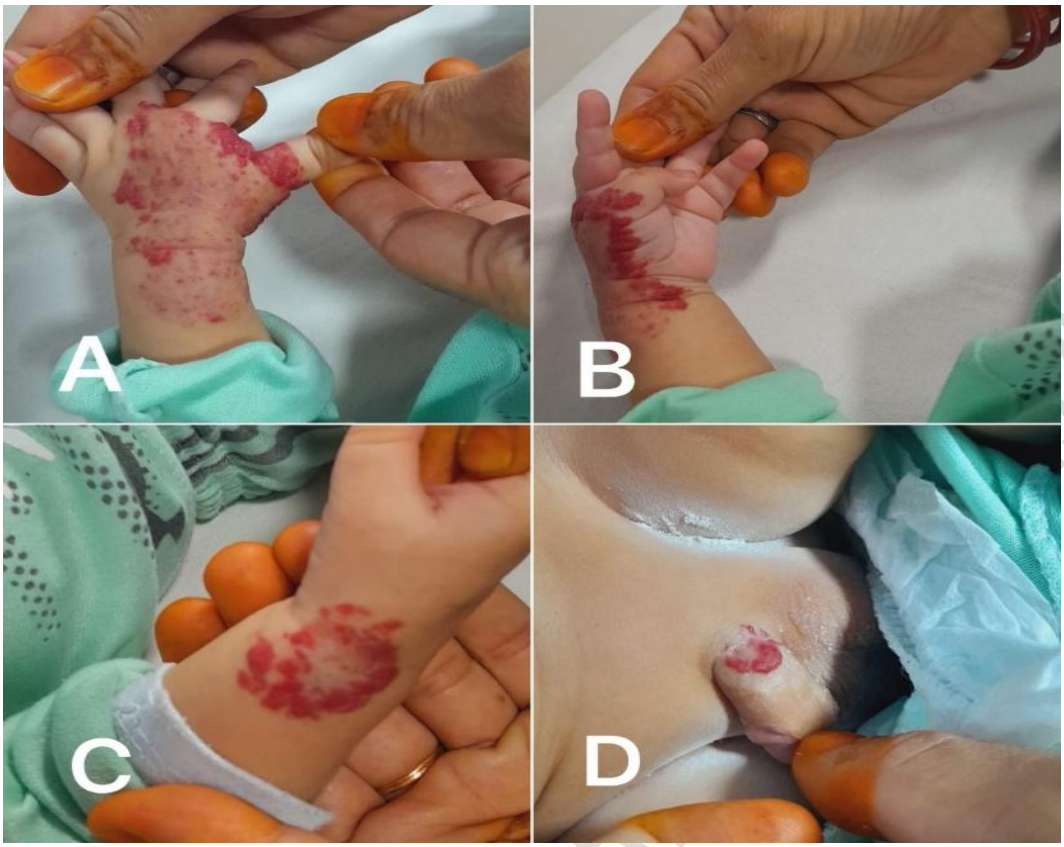

Figure 2: Case 2 (A, B) Multiple well-demarcated, erythematous soft tissue swellings, present over the dorsum of the palm and wrist area of the left hand (C) Multiple well-demarcated, erythematous soft tissue swelling over the dorsal aspect of right wrist (D) well-demarcated, erythematous soft tissue swellings present at the base of the penis.

Discussion

Infantile Hemangiomas (IH) arehamartomatous, benign vascular tumors, arising from endothelial proliferation forming multiple blood-filled cavities. Infantile Hemangioma can be classified into superficial cutaneous IH, with papillary and reticular dermis involvement and deep cutaneous IH, with reticular dermis and subcutaneous tissue infiltration. [9]Among all soft-tissue tumors, Hemangiomas contribute to 7%, whereas intramuscular hemangiomas are comprised of 0.8% of all hemangiomas. [10]The most frequently affected location of these lesions are the head and neck followed by the trunk. [4] Limbs and perineum are among the least commonly involved sites, however, involvement of these locations(limbs, wrist and genitalia) was observed in our patients, which is rare. 45% of these lesions are found in lower extremity, [10] however, our patient presented with upper extremity lesion. Even though our patient (case 2)was a male, hence it is not consistent with literature, as hemangiomas are more frequently presented in females with female to male ratio being 3–5:1 and it correlate with our

case 1. Diagnosis of IH is clinical, however when diagnosis is uncertain, imaging modalities like ultrasonography and MRI can be used. Imaging typically demonstrates a solid, well-circumscribed mass with high-flow vascularity on Doppler ultrasonography. On MRI, it usually appears as a well-defined mass that is isointense to muscle on T1, hyperintense on T2, with flow voids. [2] The diagnosis was made clinically in our patients, and imaging studies were not performed because of the non-affordability of the patient.

The patient in case 1 presented with an IH over the deltoid region. Although IH involving limbs is not entirely uncommon, this particular presenting location is atypical especially with concomitant swelling of the surrounding area. It is crucial to differentiate infantile hemangioma from an infantile fibrosarcoma. Although similar in appearance, key exam findings like firmness, spherical/protruding and grotesque appearance can point towards an alternate diagnosis of infantile fibrosarcoma, [10] which was incongruent with our patient's clinical findings. Another differential diagnosis is a NICH (Non-involuting congenital hemangioma) which grows in utero and is present at birth[8] and can be differentiated from IH on the basis of a careful history and examination as well. Other possible differentials include infection, trauma, kaposiform hemangioendothelioma, tufted angioma and pyogenic granuloma. [11]Approximately 27% of intramuscular hemangiomas occur in the upper extremity, most commonly involving the triceps, biceps, FDS, and FDP muscles; however, in our case, the lesion is located in the deltoid muscle, which is atypical compared to the usual distribution. Only one case report by Shah et al has been publishedin Pakistan,of a 40-year-old male presenting with an upper extremity intramuscular hemangioma in the triceps muscle. [12] No literature has been identified reporting upper limb IH over the deltoid region in Pakistan as well as internationally.

The patient in case 2 presented with bilateral symmetrical superficial IH involving both wrists without restriction of wrist and thumb movements along with the dorsal aspect of left hand and genital area which is an extremely rare anatomical location for IH. There have been no reported local or international cases of bilateral symmetrical IH of the limbs, with very few cases of hemangiomas involving the wrist area, and only one reported case of isolated deep cutaneous hemangioma of the wrist. [13] Only 1% of all hemangioma cases involve the genital area, which may be associated with anorectal, urogenital and spinal anomalies but no wrist joint, finger joint and genital abnormality was noted in case 2. [14]Hemangioma of the genitalia is very rare, as found in our patient and usually spontaneously regresses so conservative treatment is generally advised. Hemangioma of the genital/perineal region is associated with PELVIS syndrome (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag). The involvement of the genital area is rare and particularly critical to recognize because of the risk of infection and ulceration, requiring early intervention with propranolol. [14,15] The combination of symmetry and genital involvement has not been described well in previous published literature, as presented in our patient (Case 2),since IHs often present as solitary/segmental lesions. A case of multiple hemangiomas of the scrotum, perineum and pelvis has

been reported by Nouira Y et.al. [16] In contrast, our case demonstrates a hemangioma at the base of the penis, which is an extremely unusualpresentation.

Abdominal ultrasonography is advised for infants <6 months with ≥5 cutaneous hemangiomas to rule out hepatic hemangiomas.[17]However, neither patient fit the criteria for screening for hepatic hemangioma, hence abdominal ultrasonography was not performed in our patients.

The hemangioma in patient 1 regressed with treatment with combination of oral steroids and topical propranolol which is consistent with known response to combination therapy for IH. [18]Patient 2 was also prescribed the same treatment however no treatment outcome data is available for comparison due being lost to follow up.

The risk factors for developing IH include female sex, low birth weight, progesterone intake, miscarriage history, anemia in pregnancy, PPROM (preterm premature rupture of membranes), placenta previa, PROM (premature rupture of membranes) and abnormal amniotic fluid volume. [19,20]Risk factors such as female gender and low birth weight (2.3 kg at birth) were identified in Patient 1. In contrast, Patient 2 had no significant risk factors; however, the presentation in a male patient was atypical, as IH is more commonly observed in females, with limited supporting evidence in the existing literature for such a presentation.

IH is associated with serum markers like GLUT-1, IGF-2, VEGF-A with a positive correlation between disease severity and serum marker levels. [21] There are a few suggested hypotheses for the pathogenesis of IH. Hypoxia induced expression of hypoxia-inducable factor-2 alpha (HIF-2 alpha) and suppression of aldehyde dehydrogenase 1 (ALDH1A1), migration of placental origin IH stem cells supported by presence of circulating levels of Chromosome 19 miRNA cluster (C19MC) microRNA, as well as elevated levels of ACE (angiotensin converting enzyme) and AGTR1 (angiotensin II receptor type 1) are all pathogenic mechanisms hypothesized for this disease. [22] The bilaterality of the IH presenting in patient 2 suggests developmental pathology, which is consistent with current literature. However, we believe this presentation could possibly act as a phenotypic timestamp, suggesting that the pathological mechanism occurred early in development, before progenitor cells are spatially restricted. Solitary lesions, by contrast, likely result from later or localized alterations in endothelial progenitors.

Conclusion:

Infantile hemangiomas can present with atypical patterns and locations that expand the spectrum of known disease manifestations. Recognition of such uncommon manifestations is essential to avoid misdiagnosis, exclude important mimics, anticipate common complications and initiate timely treatment, particularly in anatomical sites with high risk of complications. These observations support a possible developmental basis for symmetric lesions and underscore the need for further reporting and study of rare infantile hemangioma phenotypic presentations.

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Conflict of Interest:

There is no conflict of interest among all authors.

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Ethical Considerations:

The research adhered to the ethical framework. Participant was comprehensively informed about the study's objective and the researcher's role, ensuring transparency. Informed consent was obtained from the patient. Anonymity and confidentiality were upheld.

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