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SYSTEMATIC REVIEW

Sirolimus for diffuse intestinal infantile hemangioma with PHACE features: systematic review

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BACKGROUND: We report a 3-month-old female with cardiovascular anomalies and diffuse intestinal infantile hemangioma (IIH) of the small bowel suggesting possible diagnosis of PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies). The GI symptoms persisted under treatment with propranolol, whereas the addition of sirolimus led to regression of the IIH.

METHODS: A systematic review was conducted using PubMed, EMBASE, and Ovid MEDLINE databases between 1982 and 2021.

RESULTS: A total of 4933 articles were identified; 24 articles met inclusion criteria with 46 IIH cases. The most common GI presentations were unspecified GI bleed (40%) and anemia (38%). The most common treatments were corticosteroids (63%), surgical resection (32.6%), and propranolol (28%). Available outcomes were primarily bleeding arrest (84%). Nine cases (19.5%) were diagnosed with definite PHACE, 5 (11%) with possible PHACE, and 32 (69.5%) no PHACE. Our case presented with symptoms most consistent with those of possible PHACE and definite PHACE. No cases in this review underwent treatment with sirolimus.

CONCLUSIONS: This is the first reported case of successful treatment of IIH with sirolimus. Our case, along with other patients who present with IIH and PHACE features, suggests consideration of IIH as a diagnostic criterion for PHACE syndrome.

Pediatric Research (2023) 93:1470–1479; https://doi.org/10.1038/s41390-022-02325-z

IMPACT:

- This is the first reported case in which sirolimus showed regression of an intestinal infantile hemangioma.
- This study serves to demonstrate the presentation, treatment, outcomes of intestinal infantile hemangioma, and correlation with PHACE.
- The potential correlation between intestinal infantile hemangioma and PHACE deserves more study in consideration of intestinal infantile hemangioma as a diagnostic criterion of PHACE.

INTRODUCTION

Infantile hemangioma (IH) is the most common pediatric vascular tumor, with a reported incidence between 2 and 10%.[1,2] The liver is the most common extracutaneous location for IH, followed by the gastrointestinal tract, brain, mediastinum, and lungs.[3] A subgroup of patients with infantile hemangiomas exhibits associated structural anomalies of the brain, cerebral vasculature, eyes, aorta, and chest wall in the neurocutaneous disorder named PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies).[4,5]

According to the revised diagnostic criteria proposed in 2016,[6] the diagnosis of definite-PHACE requires either the presence of a facial hemangioma >5 cm in diameter, plus one major or two minor criteria or a hemangioma of the neck, upper trunk or trunk and proximal extremity plus two major criteria. Alternatively, the diagnosis of possible-PHACE can be made without meeting all the aforementioned criteria. If a patient lacks the presence of a cutaneous hemangioma, a diagnosis of possible-PHACE can be made if two major criteria are met (Supplement A). Characterization of clinical features of PHACE has been made by frequency across the following organ systems: arterial, structural brain, cardiovascular, ocular, midline, neurologic signs and symptoms, endocrine, hemangioma-related complications, and miscellaneous. Hemangioma-related complications including impairment of the visual axis, stridor, and ulceration are considered "less common," whereas gastrointestinal (GI) bleeding from hemangiomas is considered "rare" (Supplement B).[6]

We hypothesize that, despite the lack of cutaneous involvement, the presentation of our patient is more consistent with findings seen in patients diagnosed with definite- or possible-PHACE when compared to patients not diagnosed with PHACE. In this systematic review, we aim to determine: (1) how often patients with infantile intestinal hemangioma (IIH) exhibit diagnostic and/or clinical features of PHACE and (2) the current treatments and outcomes for IIH.

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Received: 15 July 2022 Revised: 1 September 2022 Accepted: 13 September 2022
Published online: 30 September 2022

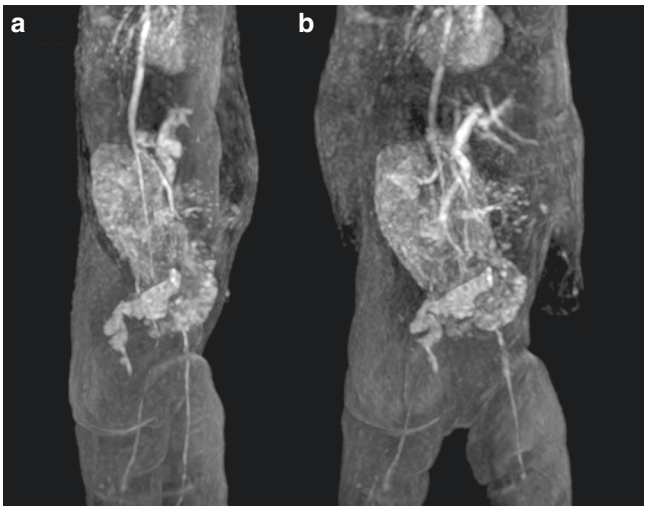

Fig. 1 Diagnostic MRI of our 3-month-old patient's intestinal hemangioma prior to treatment. Abdominal T2-weighted MRI demonstrating extensive hemangioma involvement of the small bowel and mesentery with enlargement of the superior mesenteric artery and vein (**a**: transverse view; **b**: anteroposterior view).

CASE REPORT

A 3-month-old female with a prenatal diagnosis of right aortic arch, aberrant left subclavian artery (ALSA), ventricular septal defect (VSD), and patent foramen ovale (PFO) presented to the emergency department with 3 weeks of pallor, restlessness around feeding, and failure to gain weight. Weight on admission was 5.22 kg (25th percentile). Initial work-up was notable for hemoglobin 7.1 g/dL, which dropped to 6.0 g/dL during admission, prompting blood transfusion. Labs were significant for a reticulocyte count of 144 k/μL and a haptoglobin of 406 mg/dL, consistent with active bleeding and hypo-proliferation.

Abdominal ultrasound was performed after the patient exhibited continued restlessness around eating, demonstrating impressive fullness in lower left abdomen, medial to left kidney, in which a 7–8 cm collection of blood vessels passed with no clear boundaries. Computed tomography (CT) of the chest and abdomen showed strong centralized destruction at the level of the adrenal gland, left pancreas, and other retroperitoneal processes, with some free fluid and no evidence of hepatosplenomegaly. Abdominal magnetic resonance imaging (MRI) demonstrated high signal intensity on T2-weighted imaging (Fig. 1), demonstrating extensive involvement of the small bowel and mesentery. Full-body MRI excluded additional involvement in the brain, chest, abdomen, and pelvis. A small core biopsy of the mass retrieved under ultrasound visualization revealed a vascular neoplasm composed of delicate capillaries with closely packed blood vessels, lined by cytologically bland endothelium. GLUT-1, CD34, and CD31 staining were positive, and podoplanin (D2–40) was negative, suggestive of an infantile hemangioma (IH). No cutaneous hemangiomas were noted on physical exam. Ophthalmology exam was normal.

The patient began treatment with propranolol 1.5 mg/kg/day and was gradually increased to 3.0 mg/kg/day over 2 weeks with no adverse events. After 1 month of treatment, the patient was readmitted due persistent anemia, suggesting continued bleeding. Rescue therapy was initiated with sirolimus 0.4 mg/m^2 twice daily while continuing propranolol treatment and the patient was stabilized and discharged. Overall, sirolimus was well tolerated. The patient experienced episodes of mild fatigue and reduced appetite that may have been associated with treatment. During this time, propranolol was maintained at 3.0 mg/kg/day. After 2 months of both sirolimus and propranolol as an outpatient, the patient successfully reached a weight of 7.7 kg (52nd percentile) and maintained an acceptable hemoglobin level of 11.2 g/dL. Lipid profile remained within normal limits throughout treatment. Repeat abdominal ultrasound showed no evidence of excess fluid in peritoneum, almost complete regression of the intestinal wall thickening, and reduction of the abdominal mass. At 3-month follow-up, the small bowel hemangioma measured 25 × 22 × 32 mL, compared to 40 × 30 × 48 mL at baseline.

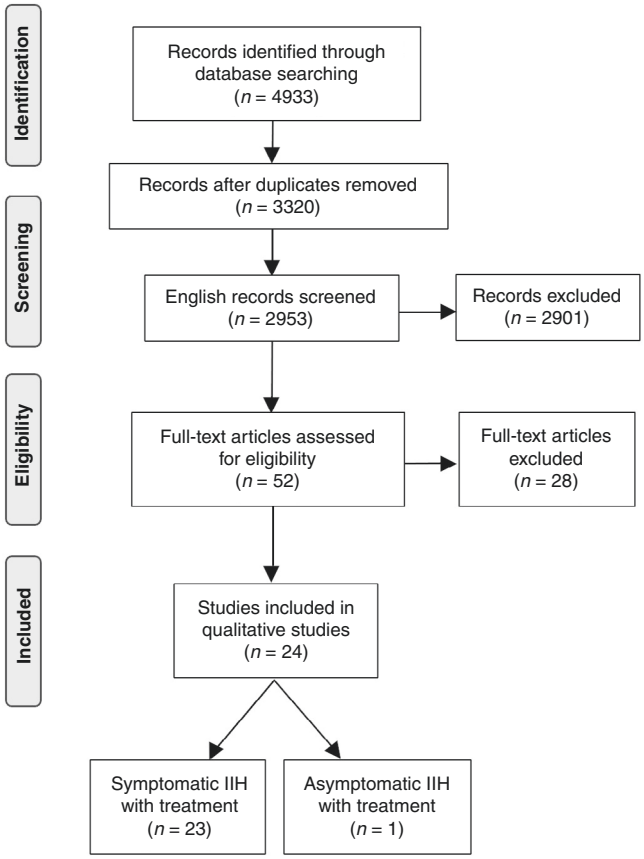

Fig. 2 PRISMA search strategy. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of literature search strategy.

SYSTEMATIC LITERATURE REVIEW

Methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) and was registered at the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021256217).[7] The last search was conducted on May 28, 2021. We used the databases PubMed, EMBASE, and Ovid MEDLINE, between the years 1982 and 2021, with the following search terms: (hemangioma OR haemangioma OR haemangiomata) AND (intra-abdominal OR GI OR gastrointestinal OR intestinal OR small bowel). Two reviewers (SG and EK) independently screened titles and abstracts to assess for inclusion in the Rayyan Software and were blinded to each other's inclusion and exclusion decisions.[8] Case reports, case series, randomized control studies, retrospective reviews, and clinical trials were included if they pertained to IIH based on typical clinical dynamics and/or histology and included data points related to patient demographics, clinical characteristics, and treatment management. Patients who presented with intestinal hemangiomas before the age of 5 years were included. We excluded non-English articles,

literature reviews, systematic reviews, meta-analyses, and surveys. Cases were excluded if the location of the GI tract was not specified. Non-infantile (e.g., cavernous) or otherwise unspecified subtypes of hemangiomas were excluded.

After unblinding the final decisions, disagreements were resolved with discussion and detailed analysis of the studies in question. The same reviewers extracted data from relevant articles pertaining to demographic data, IIH, PHACE, treatment, and outcome. Extracted data were documented in Microsoft Excel, version 3.04.

RESULTS

The literature search yielded 24 included articles (Fig. 2). Among these, 46 of 111 cases met inclusion criteria for IIHs (Table 1). Data related to the presence and absence of PHACE features, diagnosis, and cutaneous hemangiomas for the included cases of IIH can be found in Table 2. Specific PHACE features and location of cutaneous hemangiomas are further defined in Table 3. Patients were predominantly female ($n = 37/45$, 82%). Only 1 case (2%) did not present with GI symptoms. Of the symptomatic patients, average age of GI symptom presentation was 5.2 months (range: birth–5 years).

A total of 9 cases (19.5%) were diagnosed with definite-PHACE, 5 (11%) possible-PHACE, and 32 (69.5%) no-PHACE. The varying IIH presentations, treatments, and outcomes are organized by PHACE diagnosis in Table 4. Overall, the most common GI presentations were unspecified GI bleed ($n = 18/45$, 40%), anemia ($n = 17/45$, 38%), melena ($n = 10/45$, 22%), FTT ($n = 7/45$, 15.5%), and vomiting ($n = 7/45$, 15.5%). The most common treatments were corticosteroids ($n = 29/46$, 63%), surgical resection ($n = 15/46$, 32.6%), propranolol ($n = 13/46$, 28%), vincristine ($n = 7/46$, 15%), and RBC transfusion ($n = 7/46$, 15%). No cases in this systematic review underwent treatment with sirolimus for IIH. Outcomes were available for 25 of the symptomatic cases, which were primarily bleeding arrest ($n = 21/25$, 84%) and infrequently, ongoing bleeding ($n = 1/25$, 4%) and death ($n = 3/25$, 12%). Clinical features of PHACE by organ system were primarily hemangioma related ($n = 46/46$, 100%), followed by arterial ($n = 10/46$, 22%), cardiovascular ($n = 9/46$, 19.6%), ocular ($n = 8/46$, 9%), endocrine ($n = 3/46$, 6.5%), structural brain ($n = 3/46$, 6.5%), midline ($n = 2/46$, 4%), neurological ($n = 2/46$, 4%), and miscellaneous abnormalities ($n = 2/46$, 4%).

Cardiovascular involvement was most commonly seen in cases with definite PHACE ($n = 7/9$, 78%). Of the available data, death/ongoing bleeding were only reported in cases with possible PHACE ($n = 1/2$, 50%) or no PHACE ($n = 3/18$, 17%). The presenting symptoms of our patient was most commonly seen in cases of possible PHACE (anemia 40%, FTT, 40%) and definite PHACE (pallor 11%). Our patient's outcome of bleeding arrest was most frequently seen in cases with definite PHACE (55.6%). Aside from hemangioma-related complications, our patient's cardiovascular involvement was most frequently seen in cases with definite PHACE (77.8%).

DISCUSSION

We present a case of an infant with right aortic arch, aberrant left subclavian artery, VSD, and IIH causing anemia and FTT. We hypothesize that our patient's extreme presentation of a large symptomatic hemangioma in the context of cardiac malformations is not likely due to chance, but rather, due to the association of PHACE syndrome. However, based on the current diagnostic criteria for PHACE, our patient only meets one major (aberrant left

Table 1. Included studies and number of cases that met inclusion criteria for treated infantile intestinal hemangioma.

Author (year)	Country	Study type	Total # of patients reported	# Patients met inclusion criteria (%)
Al-Mushali et al.[21]	Oman	Case Report	1	1 (100)
Bank et al.[22]	United States	Case Series	2	2 (100)
Chattopadhyay et al.[23]	India	Case Report	1	1 (100)
Coleman et al.[24]	United States	Case Report	1	1 (100)
Destro et al.[25]	Italy	Case Series	2	2 (100)
Drolet et al.[26]	United States	Case Series	10	5 (50)
El Hassan et al.[27]	United States	Case Report	1	1 (100)
Fishman et al.[28]	United States	Case Series	21	1 (5)
Fu et al.[29]	China	Case Report	1	1 (100)
Hayek et al.[30]	United States	Case Report	1	1 (100)
Jarvi et al.[31]	United Kingdom	Case Report	1	1 (100)
Kella et al.[32]	Pakistan	Case Report	1	1 (100)
Krick et al.[33]	United States	Case Report	1	1 (100)
Madan et al.[34]	United Kingdom	Case Report	1	1 (100)
Metry et al.[35]	United States	Case Series	32	1 (3)
Morris et al.[36]	United States	Case Report	1	1 (100)
Parra et al.[37]	Canada	Case Report	1	1 (100)
Patel et al.[38]	United States	Case Report	1	1 (100)
Peterman et al.[39]	United States	Case Series	11	3 (27)
Rao et al.[40]	United States	Case Report	1	1 (100)
Scafidi et al.[41]	United States	Case Report	1	1 (100)
Shukri et al.[42]	Saudi Arabia	Case Report	1	1 (100)
Soukoulis et al.[43]	United States	Case Series	16	15 (94)
Stillman et al.[44]	United States	Case Report	1	1 (100)
		Total	111	46 (41)

Table 2. Data extraction for IIH with the presence/absence of PHACE features, diagnosis, and cutaneous hemangiomas.

	Case #	Sex	PHACE clinical features	Cut. HA	PHACE diagnosis	Age symptom onset	GI signs/symptoms	Location GI HA	Diagnostic modality	Pathology c/w IH	Treatment	Outcomes
Al-mushali et al.[21]	1	F	Present	Present	Definite	3 mo.	Projectile vomiting, abd pain, intussusception	S.I.	U/S, CT	Yes	Surgical resection, Propranolol	Bleeding arrested
Bank et al.[22]	1	F	Present	Present	Possible	5 mo.	Bloody stools, FTT, anemia	S.I., colon	Abd CTA	–	CS, TPN	Death
Bank et al.[22]	2	F	Absent	Absent	No	2 mo.	Melena, anemia	S.I.	CT	Yes	Blood transfusion, iron supplements	Bleeding arrested
Chattopadhyay et al.[23]	1	M	Absent	Absent	No	5 mo.	Intermittent bilious vomiting, FTT	S.I.	Barium follow-through, CT	Yes	Surgical resection	Bleeding arrested
Coleman et al.[24]	1	F	Absent	Absent	No	2 yr.	Bloody stools, anemia, pallor	S.I.	Meckel scan	Yes	Surgical resection, Iron	Bleeding arrested
Destro et al.[25]	1	F	Present	Absent	No	0.25 mo.	FTT, malodorous stools/ melena, emesis, abd pain, anemia	S.I.	MRI, CT	Yes	CS, surgical resection	Bleeding arrested
Destro et al.[25]	2	F	Absent	Absent	No	0.75 mo.	Melena, anemia	S.I.	Meckel scan, MRI	Yes	Surgical resection, Propranolol	Bleeding arrested
Drolet et al.[26]	1	F	Present	Present	No	0.32 mo.	Respiratory distress, labile BP, melena, anemia, FTT	S.I.	Angiogram	Yes	CS, Propranolol, Vincristine	Ongoing intermittent GI bleeding at 2 years
Drolet et al.[26]	2	F	Present	Present	Definite	0.55 mo.	Bloody stools, pale, anemia	S.I.	U/S, CT	–	CS, Interferon alpha-2b, Vincristine	Bleeding arrested
Drolet et al.[26]	3	F	Present	Present	Definite	6 mo.	intermittent melena	S.I.	All negative	Yes	CS, surgical resection, Vincristine, packed RBC	Bleeding arrested
Drolet et al.[26]	5	F	Present	Present	Definite	<1 yr.	GI bleed (unspec.)	S.I.	Abd CTA, Abd MRI/ A	–	CS, Propranolol	–
Drolet et al.[26]	7	F	Present	Present	Definite	Infant, unspec.	NEC presentation	S.I.		–	CS	–
El Hassan et al.[27]	1	F	Absent	Absent	No	1.3 mo.	Abdominal distension, bloody stools, hematochezia, anemia	S.I.	Abd CTA	–	Propranolol, enteral feeding	Bleeding arrested
Fishman et al.	4	M	Absent	Absent	No	1 mo.	GI bleed (unspec.)	S.I.	–	–	CS, Interferon	Death
Fu et al.[29]	1	F	Absent	Absent	No	5 yr.	Abdominal pain, vomit, anemia, small bowel obstruction	S.I.	CT	Yes	Surgical resection, iron	Bleeding arrested
Hayek et al.[30]	1	F	Absent	Absent	No	4 mo.	Melena, diarrhea, anemia	S.I.	None	Yes	Surgical resection	Bleeding arrested
Jarvi et al.[31]	1	F	Absent	Absent	No	3 mo.	Melena, FTT, pallor, anemia	S.I.	Meckel scan, angiography	Yes	Thalidomide, somatostatin analog	Bleeding arrested
Kella et al.[32]	1	F	Absent	Absent	No	2 yr.	Acute abdomen/ intussusception	S.I.	Plain abd. radiograph	Yes	Surgical resection	Bleeding arrested
Krick et al.[33]	1	F	Present	Absent	No	1.7 mo.	Feeding intolerance, abd. distension, bloody stools, anemia	S.I.	U/S, MRI	Yes	Omentectomy, Propranolol, enteral feeding	Bleeding arrested
Madan et al.[34]	1	F	Present	Present	Definite	3.2 mo.	BRBPR, anemia	S.I., liver	U/S, Abd CTA	–	CS, PPI, RBC transfusions	Bleeding arrested
[a]Metry et al.[35]	12	-	Present	Present	Definite	Infant, unspec.	NA	S.I.	MRA	–	CS, propranolol, vincristine	NA
Morris et al.[36]	1	M	Absent	Absent	No	1.5 mo.	BRBPR, weak, feeding intolerance, anemia, melena	S.I.	Abd MRI	Yes	CS, Propranolol, TPN	Bleeding arrested
Parra et al.[37]	1	F	Absent	Absent	No	Birth	GI bleed (unspec.)	S.I.	CTA	Yes	–	–
Patel et al.[38]	1	F	Present	Present	Definite	0.75 mo.	Melena, anemia	S.I.	Endoscopy		CS, Interferon alpha-2a, packed RBC	Bleeding arrested
Peterman et al.[39]	1	F	Present	Present	Possible	1 mo.	Abdominal distension, dyspnea, FTT, vomiting, poor feeding	S.I.	KUB, CT, MRI	Yes	CS, surgical resection	–
Peterman et al.[39]	2	F	Present	Present	No	2 mo.	Hematochezia	S.I.	MRI	–	CS, Vincristine, RBC transfusion	–

Table 2. continued

	Case #	Sex	PHACE clinical features	Cut. HA	PHACE diagnosis	Age symptom onset	GI signs/symptoms	Location GI HA	Diagnostic modality	Pathology c/w IH	Treatment	Outcomes
Peterman et al.[39]	11	F	Absent	Absent	No	Birth	Hematochezia	S.I.	MRI	–	Propranolol	Bleeding arrested
Rao et al.	1	F	Absent	Absent	No	1.25 mo.	Non-bilious emesis, chronic constipation, FTT, anemia	S.I.	Plain abd. radiograph	Yes	Surgical resection	Bleeding arrested
Scafidi et al.[40]	1	M	Absent	Present	No	0.75 mo.	Hyperbilirubinemia, bloody stools, anemia,	S.I.	CECT	Yes	CS, Interferon alpha-2b, transfusions, TPN	Death
Shukri et al.[41]	1	M	Absent	Absent	No	1 mo.	Fever, abd. distension, bilious vomiting, diarrhea	S.I.	Plain abd. radiograph	Yes	Surgical resection	Bleeding arrested
Soukoulis et al.[43]	1	F	Absent	Absent	No	4 mo.	GI bleed (unspec.)	S.I.	Angiogram	–	CS	–
Soukoulis et al.[43]	2	F	Absent	Absent	No	0.25 mo.	GI bleed (unspec.)	S.I.	U/S, CT	Yes	CS	–
[b]Soukoulis et al.[43]	3	F	Present	Absent	No	4 mo.	GI bleed (unspec.)	S.I.	–	Yes	CS, Propranolol	–
Soukoulis et al.[43]	4	F	Absent	Absent	No	4 mo.	GI bleed (unspec.)	S.I.	U/S, CT	–	CS	–
Soukoulis et al.[43]	5	F	Absent	Absent	No	1 mo.	GI bleed (unspec.)	S.I.	–	Yes	CS, Propranolol	–
Soukoulis et al.[43]	6	F	Present	Absent	No	<1 mo.	GI bleed (unspec.)	S.I.	U/S, MRI	–	CS	–
Soukoulis et al.[43]	7	F	Present	Absent	No	~0.7 mo.	GI bleed (unspec.)	S.I.	U/S, MRI	–	Propranolol	–
Soukoulis et al.[43]	9	F	Absent	Present	No	Birth	GI bleed (unspec.)	S.I.	Colonoscopy	Yes	CS, surgical resection	–
Soukoulis et al.[43]	10	F	Present	Present	Possible	2 mo.	GI bleed (unspec.)	S.I.	CT	–	CS, Vincristine	–
Soukoulis et al.[43]	11	F	Absent	Present	No	0.75 mo.	GI bleed (unspec.)	S.I.	CT, MRI	Yes	CS	–
Soukoulis et al.[43]	12	F	Present	Present	Possible	3 mo.	GI bleed (unspec.)	S.I.	CT	Yes	CS, surgical resection	–
Soukoulis et al.[43]	13	F	Present	Present	Definite	16 mo.	GI bleed (unspec.)	S.I.	Capsule endoscopy, CT, MRI, angiogram	–	None	–
Soukoulis et Al [43]	14	F	Absent	Present	No	2 yr.	GI bleed (unspec.)	S.I.	Tagged nuclear scan	–	CS, Interferon	–
Soukoulis et al.[43]	15	M	Absent	Present	No	0.5 mo.	GI bleed (unspec.)	S.I.	CT, U/S	–	CS, Propranolol	–
Soukoulis et al.[43]	16	M	Absent	Present	No	<1 mo.	GI bleed (unspec.)	S.I.	MRI	–	CS, Vincristine	–
Stillman et al.[44]	1	M	Present	Present	Possible	0.63 mo.	Melena, anemia	S.I.	Mesenteric arteriogram	Yes	CS, PPI, iron, transfusions	Bleeding arrested

[a]Asymptomatic or IIH with the presence/absence of PHACE features and diagnosis.
[b]Could be considered possible-PHACE if intestinal IH were counted as the diagnostic hemangioma.

Table 3. Data extraction for IIH with defined PHACE-related features.

	Case	Sex	Arterial anomaly	Structural		Ocular	Midline	Neuro	Endo	HA-related complications	Misc	Location of cutaneous hemangioma	PHACE diagnosis
				Brain	CV								
Al-mushali et al.[21]	1	F	Y	Y	–	Y	–	–	–	Y	–	Right cheek, periorbital, temple, shoulder, upper back	Definite
Bank et al.[22]	1	F	–	Y	–		–	–	–	Y	–	Right periorbital area, right forehead, lips	Possible
Bank et al.[22]	2	F	–	–	–	–	–	–	–	Y	–	NA	No
Chattopadhyay et al.[23]	1	M	–	–	–	–	–	–	–	Y	–	Left upper eyelid and orbit, left cheek, left scalp, temporal scalp, left jaw, left neck	No
Coleman et al.[24]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Destro et al.[25]	1	F	–	–	–	–	–	Y	–	Y	–	NA	No
Destro et al.[25]	2	F	–	–	–	–	–	–	–	Y	–	NA	No
Drolet et al.[26]	1	F	Y	–	–		–	–	–	Y	–	Left cheek, left preauricular region, left ear and scalp (left S2, left S3)	No
Drolet et al.[26]	2	F	Y	–	Y		–	–	–	Y	–	Bilateral periorbital regions, lower lip (bilateral S1, bilateral S3)	Definite
Drolet et al.[26]	3	F	Y	–	Y	Y	–	–	–	Y	–	Left forehead, left upper eyelid, left cheek, entire lower lip (S3), anterior and posterior neck (left S1, left S2, bilateral S3)	Definite
Drolet et al.[26]	5	F	Y	–	Y		–	–	–	Y	–	Left forehead (S1) and left chin, cheek (S3), ear and scalp, posterior neck (left S1, bilateral S3)	Definite
Drolet et al.[26]	7	F	–	–	Y		–	–	–	Y	–	Left forehead, cheek, ear, upper lip, tongue (left S1, S2, S3)	Definite
El Hassan et al.[27]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Fishman et al.[28]	4	M	–	–	–	–	–	–	–	Y	–	NA	No
Fu et al.[29]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Hayek et al.[30]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Jarvi et al.[31]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Kella et al.[32]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Krick et al.[33]	1	F	–	–	–	–	–	–	Y	Y	–	NA	No
Madan et al.[34]	1	F	Y	Y	Y	–	–	–	–	Y	–	Left upper eyelid	Definite
[a]Metry et al.[35]	12	–	Y	–	–	–	–	–	–	Y	–	Right S1	Definite
Morris et al.[36]	1	M	–	–	–	–	–	–	–	Y	–	NA	No
Parra et al.[37]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Patel et al.[38]	1	F	Y	–	Y	–	Y	–	–	Y	–	Left cheek, scalp, neck	Definite
Peterman et al.[39]	1	F	–	–	–	–	–	–	–	Y	Y	Left temple, left cheek	Possible
Peterman et al.[39]	2	F	–	–	–	–	–	–	–	Y	–	Lower lip, right cheek, right postauricular area, bilateral neck	No
Peterman et al.[39]	11	F	–	–	–	–	–	–	–	Y	–	NA	No
Rao et al.[40]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Scafidi et al.[41]	1	M	–	–	–	–	–	–	–	Y	–	Right buttock	No
Shukri et al.[42]	1	M	–	–	–	–	–	–	–	Y	–	NA	No
Soukoulis et al.[43]	1	F	–	–	–	–	–	–	–	Y	–	NA	No
Soukoulis et al.[43]	2	F	–	–	–	–	–	–	–	Y	–	NA	No
[b]Soukoulis et al.[43]	3	F	–	–	Y	–	–	–	–	Y	–	NA	Possible

Table 3. continued

	Case	Sex	Arterial anomaly	Structural		Ocular	Midline	Neuro	Endo	HA-related complications	Misc	Location of cutaneous hemangioma	PHACE diagnosis
				Brain	CV								
Soukoulis et al.[43]	4	F	–	–	–	–	–	–	–	Y	–	NA	No
Soukoulis et al.[43]	5	F	–	–	–	–	–	–	–	Y	–	NA	No
Soukoulis et al.[43]	6	F	–	–	–	–	–	–	–	Y	Y	NA	No
Soukoulis et al.[43]	7	F	–	–	–	–	Y	–	–	Y	–	NA	No
Soukoulis et al.[43]	9	F	–	–	–	–	–	–	–	Y	–	Left forehead, temple, maxillary	No
Soukoulis et al.[43]	10	F	–	–	Y	–	–	–	–	Y	–	Lower lip, right preauricular, left neck	Possible
Soukoulis et al.[43]	11	F	–	–	–	–	–	–	–	Y	–	Lower lip, submental	No
Soukoulis et al.[43]	12	F	–	Y	–	–	–	–	Y	Y	Y	Orbit, temporal, parotid, scalp	Possible
Soukoulis et al.[43]	13	F	Y	–	Y	Y	–	Y	Y	Y	–	Right cheek, periorbital, temple, shoulder, upper back	Definite
Soukoulis et al.[43]	14	F	–	–	–	–	–	–	–	Y	–	Right forehead, periorbital, maxillary	No
Soukoulis et al.[43]	15	M	–	–	–	–	–	–	–	Y	–	Multifocal	No
Soukoulis et al.[43]	16	M	–	–	–	–	–	–	–	Y	–	Multifocal	No
Stillman et al.[44]	1	M	–	–	–	Y	–	–	–	Y	–	Right face, scalp, ear, nasal tip, upper lip and smaller areas of the left face, scalp, and posterior palate	Possible

Abd abdominal, *BRBPR* bright red blood per rectum, *BP* blood pressure, *C/w* consistent with, *CECT* contrast-enhanced computed tomogram, *CS* corticosteroid, *CT* computed tomography, *CTA* computed tomography with angiography, *CV* cardiovascular, *Endo* endocrinologic symptoms, *F* female, *FTT* failure to thrive, *GI* gastrointestinal, *HA* hemangioma, *IH* infantile hemangioma, *IIH* infantile intestinal hemangioma, *KUB* kidney ureter bladder X-ray, *M* male, *Misc* miscellaneous, *Mo.* month, *MRI* magnetic resonance imaging, *NA* not applicable, *NEC* necrotizing enterocolitis, *Neuro* neurologic symptoms, *PHACE* posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies, *PPI* proton pump inhibitor, *RBC* red blood cell, *S.I.* small intestine, *S1, S2, S3* segment 1, segment 2, segment 3, *TPN* total parenteral nutrition, *Unspec.* unspecified, *U/S* ultrasound, *Y* yes, *Yr* year.

[a]Asymptomatic.

[b]Could be considered possible-PHACE if intestinal IH were counted as the diagnostic hemangioma.

Table 4. IIH clinical features, treatment, and outcomes by PHACE diagnosis.

	Definite PHACE ($N = 9$)		Possible PHACE ($N = 5$)		No PHACE ($N = 32$)	
Clinical presentation of symptomatic IIH						
Abdominal distension	0	(0%)	1	(20%)	3	(9.4%)
Anemia	3	(33.3%)	2	(40%)	12	(37.5%)
Bloody stools	1	(11.1%)	1	(20%)	3	(9.4%)
BRBPR	1	(11.1%)	0	(0%)	1	(3.1%)
Chronic constipation	0	(0%)	0	(0%)	1	(3.1%)
Diarrhea	0	(0%)	0	(0%)	2	(6.3%)
Dyspnea/respiratory distress	0	(0%)	1	(20%)	1	(3.1%)
Feeding intolerance	0	(0%)	1	(20%)	2	(6.3%)
FTT	0	(0%)	2	(40%)	5	(15.6%)
GI bleed, unspecified	2	(22.2%)	2	(40%)	14	(43.8%)
Hematochezia	0	(0%)	0	(0%)	3	(9.4%)
Hyperbilirubinemia	0	(0%)	0	(0%)	1	(3.1%)
Labile BP	0	(0%)	0	(0%)	1	(3.1%)
Melena	2	(22.2%)	1	(20%)	7	(21.9%)
NEC	1	(11.1%)	0	(0%)	0	(0%)
Painful abdomen/intussusception/acute abdomen	1	(11.1%)	0	(0%)	3	(9.4%)
Pallor/weakness	1	(11.1%)	0	(0%)	3	(9.4%)
Vomiting	1	(11.1%)	1	(20%)	5	(15.6%)
Treatments						
Corticosteroids	7	(77.8%)	1	(100%)	17	(53.1%)
Hyperalimentation/TPN	0	(0%)	1	(20%)	3	(9.4%)
Interferon	2	(22.2%)	0	(0%)	3	(9.4%)
Iron supplement	0	(0%)	1	(20%)	3	(9.4%)
No treatment	1	(11.1%)	0	(0%)	0	(0%)
Packed RBC/RBC transfusion	3	(33.3%)	1	(20%)	3	(9.4%)
PPI	1	(11.1%)	1	(20%)	0	(0%)
Propranolol	3	(33.3%)	0	(0%)	10	(31.3%)
Somatostatin analog	0	(0%)	0	(0%)	1	(3.1%)
Surgical resection	2	(22.2%)	2	(40%)	11	(34.4%)
Thalidomide	0	(0%)	0	(0%)	1	(3.1%)
Unavailable	0	(0%)	0	(0%)	1	(3.1%)
Vincristine	3	(33.3%)	1	(20%)	3	(9.4%)
Outcomes						
Bleeding arrested	5	(55.6%)	1	(20%)	15	(46.9%)
Death	0	(0%)	1	(20%)	2	(6.3%)
Ongoing bleeding	0	(0%)	0	(0%)	1	(3.1%)
NA	1	(11.1%)	0	(0%)	0	(0%)
Unavailable data	3	(33.3%)	3	(60%)	14	(43.8%)
Clinical features associated with PHACE by organ system						
Arterial abnormalities	8	(88.9%)	1	(20%)	1	(3.1%)
Structural brain	2	(22.2%)	1	(20%)	0	(0%)
Cardiovascular	7	(77.8%)	1	(20%)	1	(3.1%)
Ocular	3	(33.3%)	1	(20%)	0	(0%)
Midline	1	(11.1%)	0	(0%)	1	(3.1%)
Neurologic signs and symptoms	1	(11.1%)	0	(0%)	1	(3.1%)
Endocrine	1	(11.1%)	1	(20%)	1	(3.1%)
Hemangioma-related complications	9	(100%)	5	(100.0%)	32	(100%)
Miscellaneous	0	(0%)	1	(20%)	1	(3.1%)

subclavian artery) and two minor (aortic arch anomaly, VSD) diagnostic criteria for definite PHACE.[7] Thus, we would like to highlight the small bowel as an extra-cutaneous site in which hemangiomas may present in the context of PHACE. By excluding intestinal hemangiomas in the current diagnostic of PHACE, it is possible that diagnoses may be delayed in other similar, yet less extreme cases. With this consideration, cardiovascular or other characteristic clinical PHACE features may guide consideration of PHACE in infants with anemia who lack cutaneous hemangiomas.

If IIH were considered a defining hemangioma in the same way that head/neck hemangiomas are considered in the diagnosis of PHACE, then one case in this review with no PHACE diagnosis

would meet criteria for possible PHACE. None of the possible PHACE cases would meet criteria for definite PHACE by assuming this change. This is likely due to the fact that possible PHACE cases tended to already have cutaneous hemangiomas. However, the data in this cohort may underestimate the percentage of PHACE cases if full workups had not been performed.

Results from this review demonstrated that patients with a IIH most commonly present with anemia followed by melena, irrespective of PHACE diagnoses. Possible PHACE cases tended to present with FTT, whereas no PHACE diagnosis tended to present with vomiting. There was a higher frequency of patients with no PHACE diagnosis that underwent surgical resection as a treatment for symptomatic infantile IH. Of note, many of the included articles were published prior to the advent of the beta-blocker era. While these case series and case reports suggest positive outcomes with respect to bleeding cessation for both PHACE and non-PHACE cases using propranolol, our case suggests that sirolimus might represent an additional treatment option for non-responsive cases. Sirolimus, also known as rapamycin, is an mTOR inhibitor, has emerged as a safe and effective treatment modality for slow-flow vascular anomalies and for kaposiform emandoendothelima (KHE).[9] Few reports highlight its role in the treatment of IH.[10,11] Sirolimus might work by targeting the self-renewal of IH stem cells, diminishing differentiation, and inhibiting vasculogenesis, ultimately leading to regression of hemangioma vasculature.[12] Our case suggests that sirolimus may play a role as an adjunct to propranolol in the treatment of IIH.[13]

This study has limitations. First, as with all systematic reviews, analyzing data in this format is limited by inconsistent reporting among case reports and case series in the literature. Second, the anecdotal evidence from case series and case reports lacks scientific rigor to determine a true association between IIH and PHACE. Third, the cases included in this review may under-represent the total number cases in the literature given that cases were excluded during the review process if age, hemangioma type, or location in the GI tract were not specified.[3,14–20]

The present case is the first reported case in the literature that demonstrates sirolimus's efficacy in treating propranolol resistant IIH. It is unknown whether sirolimus was effective on its own or due to synergistic effects with propranolol. Other theories to explain our patient's resolution is that propranolol merely required additional time to take effect. If this is the case, sirolimus might play a role as a "bridge therapy" in actively bleeding, non-stable IIH patients. Future studies are required to validate our findings with a larger sample size.

DATA AVAILABILITY

The dataset generated and analyzed in this study are included in Tables 2 and 3 of this published article with appropriate citations to the original articles.

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ACKNOWLEDGEMENTS

We would like to acknowledge Tali Mualem, MD in management of this patient.

AUTHOR CONTRIBUTIONS

All authors meet the *Pediatric Research* authorship requirements.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-022-02325-z.

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