Original Article

Peripheral Arteriovenous Malformations—A Case Series

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Abstract

Context: Arteriovenous malformations (AVMs) are aggressive vascular malformations that often result in significant morbidity. Patients may present to a dermatologist due to associated skin changes. Early diagnosis is important as treatment is available to halt their progression toward irreversible destruction of adjacent tissues. **Aims:** To study the clinical profile of peripheral AVMs presenting to the dermatologist and to provide a diagnostic algorithm. **Settings and Design:** A retrospective study of patients of all age groups with peripheral AVMs who presented to the Department of Dermatology at a tertiary care hospital in India was performed. Syndromic forms were also included. **Subjects and Methods:** We conducted a search of patients with peripheral AVMs, which were seen over a period of 51 months, i.e., from July 2014 to September 2018, from electronic medical records and reviewed their clinical details. **Statistical Analysis Used:** Descriptive statistics such as frequency, mean, and median were computed. **Results:** We report a series of 13 patients with peripheral AVMs, which constituted 6.7% (13/193) of all vascular malformations during this period. Of these, 8.3% (1/12) belonged to Schobinger's stage 1, 41.7% (5/12) to stage 2, 50% (6/12) to stage 3, and one with subcutaneous involvement devoid of cutaneous changes. The most common location was the extremities, which was seen in 53.8% (7/13). Syndromic association was present in 46.2% (6/13). Management included embolization, surgery, and medical treatment. **Conclusions:** The proportion of peripheral AVMs out of all vascular malformations was similar to reported studies. The extremities were more frequently involved as compared to the head and neck. The diagnostic algorithm provided will help us to optimize investigations and direct early management.

Keywords: *Angiogram, embolization, peripheral arteriovenous malformations, syndromic*

Introduction

Arteriovenous malformations (AVMs) are complex vascular anomalies that comprise 4.7% to 15% of all vascular malformations.[1,2] They may be evident at birth in 60% of the cases.[2] The rest manifest by adolescence or adulthood. They may occur as isolated entities or as a part of syndromes with underlying genetic mutations. Somatic mutations in MAP2K1 have been identified in nonsyndromic extracranial AVMs. Syndromes with delineated mutations include capillary malformation AVM syndrome (CM-AVM) that is associated with mutations in RASA1 and EPBH4, inherited forms of Parks Weber (PW) syndrome associated with mutations of RASA1, hereditary hemorrhagic telangiectasia associated with mutations of endoglin, ALK1 and SMAD4,[3] and the PTEN hamartoma syndromes.[4] AVMs are rapidly progressive malformations causing significant pain, bleeding, and tissue destruction to name a few of their distressing complications. Early diagnosis is important to halt their progression toward irreversible destruction of the adjacent tissues. Data on the clinical and demographic profile of AVMs from the Indian subcontinent are scarce and only limited to case reports and site specific series.[5,6]

Subjects and Methods

We conducted a search of all out-patient and in-patient records in the department of dermatology between July 2014 and September 2018 over a period of 51 months. An ethical clearance was obtained from the Institutional Review Board. All diagnoses of AVMs, including syndromic forms, were included. Demographic and clinical data including history and details of physical examination, treatment, and results of investigations were abstracted from the electronic medical records and analyzed. Lesions were characterized as localized if they were confined to one

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anatomical structure or one- or two-tissue planes for the head/neck/extremity and less than 10 cm for the trunk, and as diffuse if they involved more than one anatomical structure or more than two-tissue planes for the head/neck/extremity and more than 10 cm for the trunk.[7] The radiological images were reviewed from the records in the Department of Radiology. These were analyzed again by a senior radiologist for the purpose of this study. The laboratory parameters of each patient were also reviewed. Descriptive statistics were used to report demographic and clinical findings.

Results

We report a series of 13 patients included retrospectively over a period of 51 months with clinical and imaging features of peripheral AVMs who presented to the Department of Dermatology.

Demography

AVMs constituted 6.7% (13/193) of all vascular malformations and 4.1% (13/316) of all vascular anomalies seen during the specified time period. The female:male ratio was 2:11. The mean age at presentation was 23 years (range 3-49 years). Lesions manifested at birth in 46.2% (6/13), whereas the rest had symptoms for a mean duration of 3.6 years (range 3 months to 7 years) at presentation.

Clinical features

All patients presented with swelling or enlargement of the affected site, which was painful in 53.8% (7/13) and was associated with bleeding in 46.2% (6/13). The most common location of AVMs was on the extremities with 53.8% (7/13). Lower limb involvement was noted in 30.8% (4/13), upper limb involvement in 23.1% (3/13), trunk in 15.4% (2/13), lip in 15.4% (2/13), and cephalic involvement in 15.4% (2/13) unilaterally involving the forehead and the frontal scalp in both and involving the eyelid in one patient.

The affected site showed overlying purplish red discoloration in 30.8% (4/13), angiokeratomas in 15.4% (2/13) [Figure 1] and bluish tinged dilatations in 30.8% (4/13) [Figure 2]. Two patients with PW syndrome showed large and extensive capillary malformations of the affected limb. The overlying skin was normal in 23.1% (3/13). Lesions were compressible in 38.5% (5/13), pulsatile in 30.8% (4/13), associated with a bruit/thrill in 30.8% (4/13), and 23.1% (3/13) patients with involvement of the distal extremity had associated macrodactyly.

By Schobinger's clinical grading system,[2] 8.3% (1/12) had features of stage 1, 41.7% (5/12) of stage 2, 50% (6/12) of stage 3, and one with subcutaneous involvement devoid of cutaneous changes. Sizes of the AVMs ranged from 1 cm × 1 cm on the lower lip to the largest involving the entire lower limb in PW syndrome. Localized forms comprised 46.2% (6/13) and diffuse 53.8% (7/13), of which six were syndromic.

Syndromic association was noted in 46.2% (6/13), which included CM-AVM [Figure 3a and b] and PW syndrome

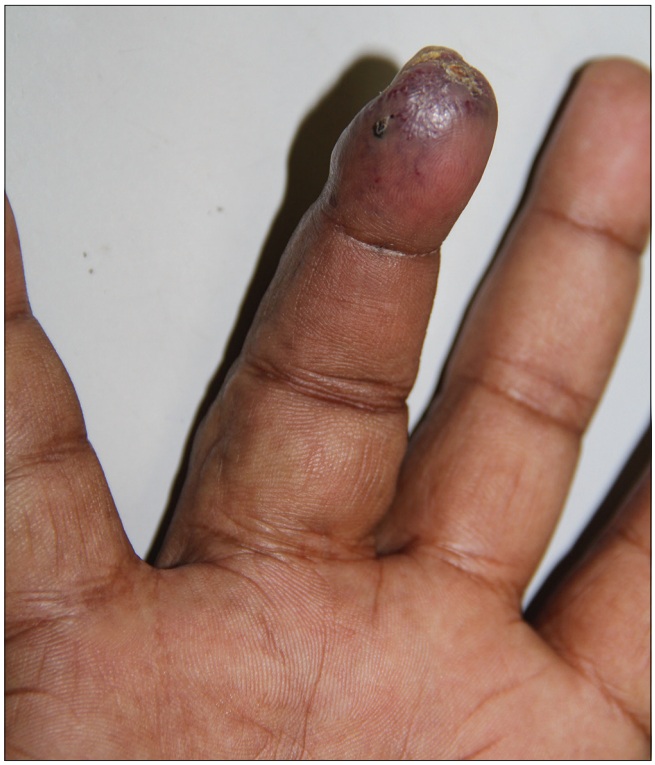

Figure 1: AVM of the right ring finger showing macrodactyly, purplish hue with angiokeratoma like papules and crusted ulcers at the distal phalange

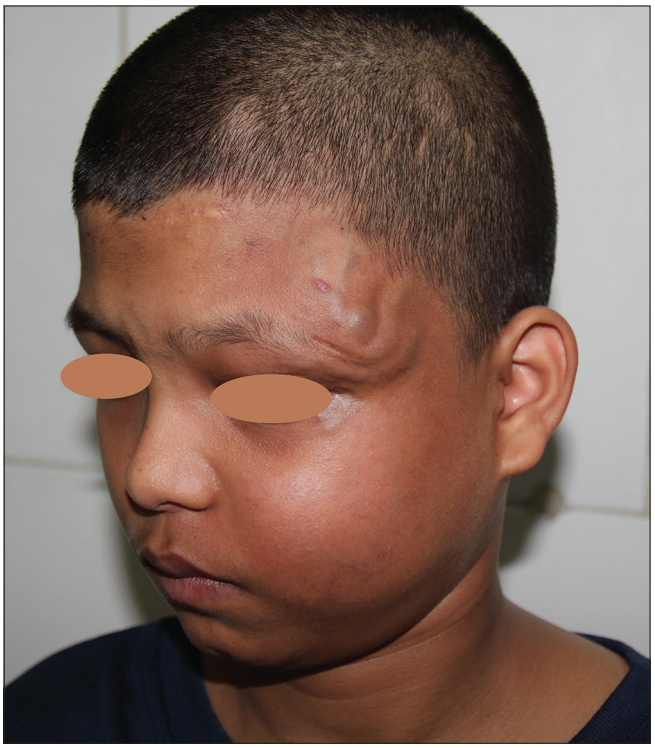

Figure 2: WB syndrome showing pulsatile, bluish tinged tortuous vessels on the left side of the forehead and frontal scalp, and ill-defined swelling of the left cheek

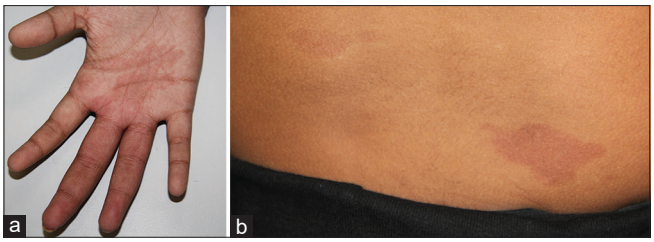

Figure 3: CM-AVM syndrome showing (a) macrodactyly of the right middle and ring fingers with overlying capillary malformation extending onto the palm; (b) capillary malformations on the lumbar areas

in 15.4% (2/13) each, Wyburn Mason (WB) syndrome [Figure 2], and Bannayan Riley Ruvalcaba (BRR) syndrome in 7.7% (1/13) each. The patient with multifocal CM-AVM was advised imaging of the brain to rule out cranial AVMs and the BRR syndrome was advised a gastrointestinal evaluation.

Investigations

Among four patients in which d-Dimer levels (normal: 0–500 ng/ml) were done, two were elevated, one with PW syndrome (586 ng/ml), and one with BRR syndrome (1079 ng/ml), suggestive of the venous component in the AVM.

Results of imaging studies

Diagnostic radiological imaging included ultrasonography (USG), Doppler, MRI, angiogram, and CT angiogram. MRI was done in 53.8% (7/13) patients; as the only diagnostic modality in four patients and in combination with angiogram in two patients and with CT angiogram in one patient. USG was done in 23.1% (3/13) patients, Doppler in 7.7% (1/13), and angiogram in 30.8% (4/13) patients in which one required a CT angiogram. These imaging modalities highlighted the high-flow nature of the malformation. Intramuscular and intraosseous involvement in WB syndrome and intraosseous involvement in CM-AVM syndrome were detected by CT angiogram [Figure 4].

Associated extracutaneous manifestations were assessed in the patient with the WB syndrome whose MRI brain revealed enlarged ophthalmic artery and veins but did not have brain parenchymal or retinal involvement.

Management

Embolization

Embolization was done in 15.4% (2/13). In one patient, there was a satisfactory improvement after one session without visible residual lesions at follow up of two years. Though the other patient had good improvement with three sessions of embolization for AVM of the great toe, his symptoms had relapsed, which required a ray amputation. Ray amputation was also done for another patient with involvement of the right ring finger. One patient with CM-AVM and another with WM syndrome declined interventional treatment with embolization.

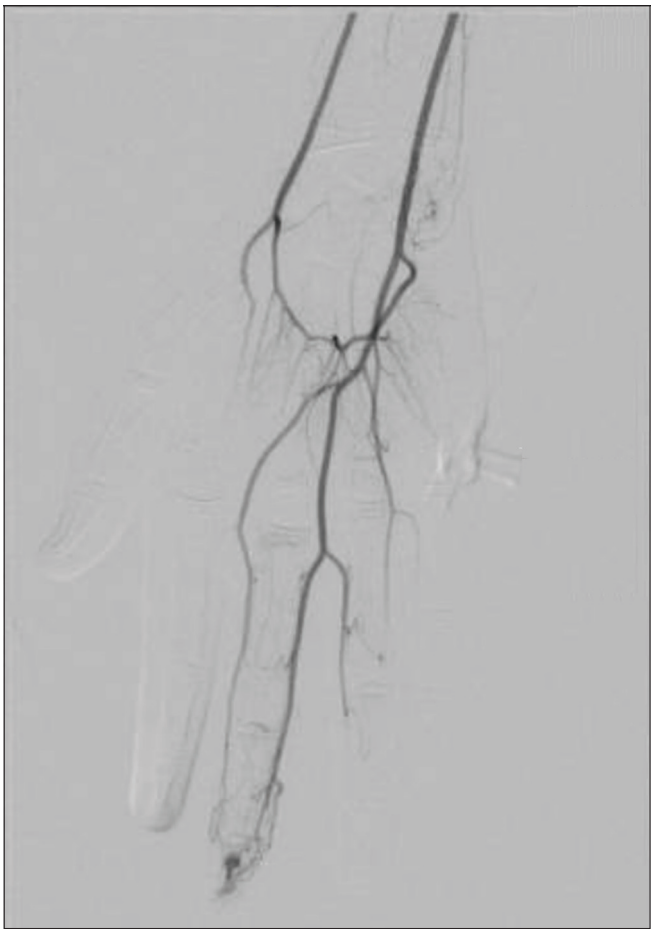

Figure 4: Selective angiogram showing hypertrophy of digital arteries to the right middle finger with a nidus at the distal phalange in the CM-AVM syndrome

Medical management

Medical treatment with sirolimus was given for the symptomatic PW syndrome and the BRR syndrome in which embolization could not be done. In the patient with PW syndrome, sirolimus was given at a dose of 0.6 mg/m^2, which was escalated 0.9 mg/m^2 once a day. This resulted in significant improvement in pain and swelling as early as one month. In the patient with BRR syndrome, sirolimus was titrated and increased to an optimum dose of 0.8 mg/m^2 twice a day, which resulted in symptomatic improvement by four months of treatment. The PW syndrome and the BRR syndrome have been on sirolimus since 14 months and 22 months, respectively till date. Follow up was advised for the PW syndrome that was asymptomatic. Five patients were lost to follow up. Investigations and interventions done are summarized in Table 1.

Discussion

AVMs located in areas other than in the brain are referred to as peripheral or extracranial AVMs.[7,8] Our series on peripheral AVMs give a detailed clinical profile of this rare entity among patients from the Indian subcontinent.

Table 1: Details of management in the series of patients with peripheral AVMs

Diagnosis	Site	d-Dimer (0-500 ng/ml)	Ultrasound	Doppler	MRI	Angiogram	CT Angiogram	Intervention
AVM*	Abdominal wall	-	-	-	-	High flow	-	One session of embolization
AVM*	Back	-	High flow	-	-	-	-	Lost to follow up
AVM*	Arm	-	-	Predominantly venous, few arterial waveforms	-	-	-	Lost to follow up
AVM*	Lower lip	-	Arteriovenous flow	-	-	-	-	Lost to follow up
AVM*	Lower lip	-	High flow	-	-	-	-	Lost to follow up
AVM*	4th finger-right	113	-	-	High flow	Diffuse nidus	-	Ray amputation
AVM*	Face	-	-	-	High flow	Nidus - frontal bone	-	Lost to follow up
PW†	Lower limb	249	-	-	High flow	-	-	Follow up advised after 1 year
PW†	Lower limb	586	-	-	High flow	-	-	Sirolimus since 14 months, up to a dose of 0.9 mg/m^2 once a day
CM-AVM‡	Hand	-	-	-	-	Nidus - distal phalange	Nidus - distal phalange	Embolization advised
CM-AVM‡	Foot	171	-	-	High flow with intra-osseous involvement	-		Embolization done thrice followed by ray amputation for relapse of symptoms
BRR§	Thigh	1079	-	-	High flow	-	-	Sirolimus since 22 months, optimized at 0.8 mg/m^2 twice daily
WM‖	Scalp, forehead	-	-	-	High flow with frontal bone involvement		High flow with frontal bone involvement	Embolization with surgery offered

* - AVM, † -PW syndrome, ‡ - Capillary malformation AVM syndrome, § - Bannayan Riley Ruvalcaba syndrome, || - WB syndrome

Early recognition is important as both medical and or interventional treatment is available to halt its progression. Dermatologists are often primary points of contact for patients with peripheral AVMs due to the associated skin changes and visibility of the lesions.

The largest series reported till date included 272 patients over a period of 18 years, which included only those with a cutaneous component and excluded the syndromic forms.[7] Another large series included 176 patients seen over a period of 14 years, which primarily focused on their management.[8] In our study, peripheral AVMs represented 6.7% of all vascular malformations similar to other studies.[1,2] Of them, 46.2% (6/13) were syndromic, the most common syndromes being CM-AVM and PW syndrome. There are sparse data on the frequency of AVMs presenting as syndromes, as most studies have excluded syndromic forms.[7] One study reports a frequency of 15.8% (3/19) of syndromic forms among cutaneous AVMs on the distal limbs.[9] In our study, the mean age at presentation was 23 years similar to other studies that report a mean age of 29.4 years.[1,8]

All the patients in our study had presented with localized or diffuse swelling, which was painful in 53.8% (7/13). A study of 19 patients with distal limb AVMs reported swelling and pain in 47% each.[9] Historically, common sites of involvement have been the head and neck region followed by the limbs, trunk, and viscera.[10] We found a higher frequency of involvement of extremities observed in 53.8% (7/13) of cases. In a series of AVMs (n = 81) of the head and neck area, congenital onset was noted in 59%.[11] We found a lower frequency with only 46.2% (6/13) of patients manifesting at birth. Clinical clues to the diagnosis of AVMs include a swelling with a vascular blush along with warmth, tenderness, pulsatility, thrill, or bruit. Presence of compressibility may vary. Clinical differentiation of early or Schobinger stage 1 AVM from a port wine stain may be difficult and radiological imaging may not always be contributory as even port wine stains with nodular hyperplasia have been detected with high-flow pattern.[12] Based on the extent of involvement, these have been classified as localized and diffuse.[7,8] We found that 85.7% (6/7) of the diffuse type were syndromic.

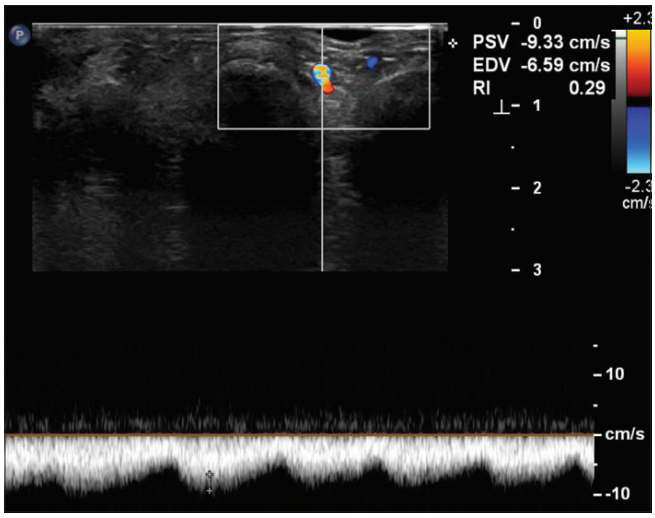

Figure 5: Axial pulse Doppler showing arterialization of the right middle finger digital vein due to shunting in the CM-AVM syndrome

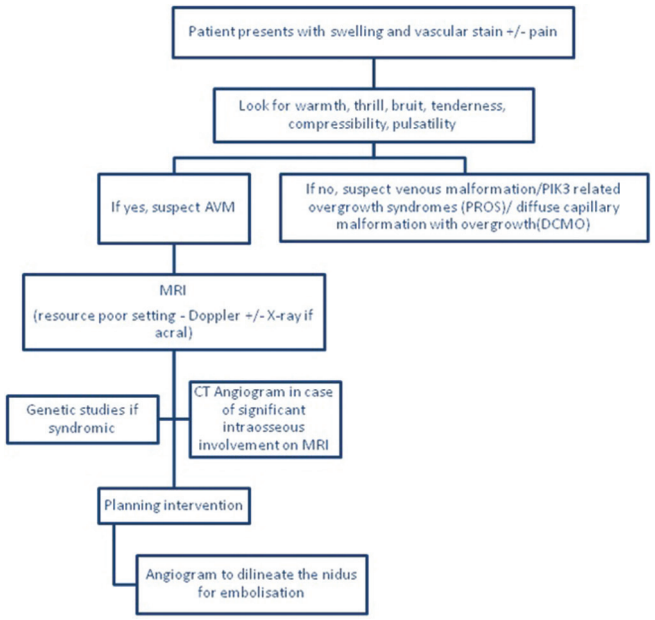

Figure 7: Diagnostic algorithm for peripheral AVMs

A thorough clinical and radiological examination is essential to detect the arterial component. Imaging is essential not only for diagnosis but also to delineate the adjacent anatomy, which is often compromised in AVMs. This will help us to optimize the treatment. Doppler demonstrates high flow with arterialization of veins [Figure 5]. High-flow pattern with flow voids is typically described on MRI [Figure 6]. MRI also demonstrates the extent of the lesion and the involvement of soft tissue structures. When there is significant intraosseous involvement detected by MRI, a CT angiogram may be useful for accurate assessment. Angiogram is essential to delineate feeder vessels and nidus prior to embolization. Based on the type of nidus detected, there are angiographic classifications described.[13]

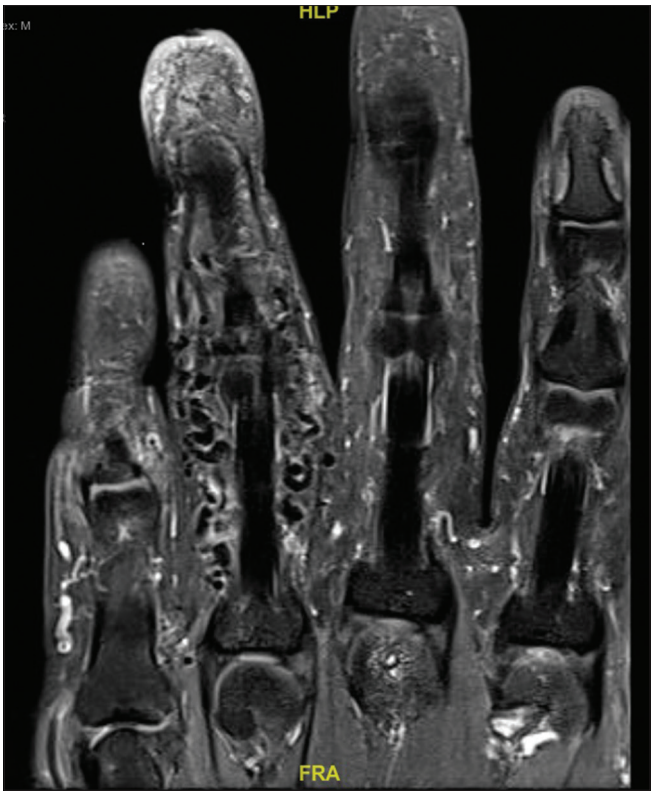

Figure 6: T2 STIR images of the right hand showing flow voids in AVM of the right ring finger

AVMs are known to expand with time, becoming complicated, and infiltrative with its growth. Hence, early intervention even for asymptomatic lesions has been suggested.[7] Management options include embolization often in a serial manner with or without surgical resection. Recurrence rates range from 8.7% to 98%,[1,7] occurring as late as ten years after starting treatment. High recurrence rates have been reported with diffuse AVMs,[14] advanced lesions, and isolated treatment with either embolization or surgery as compared to combined modalities with embolization and resection.[7] Intralesional bleomycin has been tried in Schobinger's stages 1 and 2 AVMs.[15] Pharmacotherapy is considered for complex AVMs in which intervention is not feasible. Pre- and postoperative administration of sirolimus appears to be a promising therapeutic option with success rate of up to 90% on therapy.[16] However, relapse rates off therapy need to be determined. We also found sirolimus to be effective in reducing symptoms in two patients in which neither embolization nor excision was feasible. There are reports of the use of propranolol and the use of marimastat, a metalloproteinase inhibitor.[17,18] Other medications that have been tried include tetracyclines as vasculostatic agents in brain AVMs, interferon, and VEGF (vascular endothelial growth factor) inhibitors, particularly in visceral and cranial AVMs.[19]

Conclusion

In summary, the prevalence of peripheral AVMs in our study was similar to other studies. However, a higher number of

AVMs were found on the extremities unlike other studies. Nearly half of them had a syndromic association. This study highlights the need for dermatologists to be well versed with this clinical entity, including its syndromic forms in order to optimize investigations and direct management at the earliest. We have also provided a diagnostic algorithm which can be used in the clinical setting [Figure 7].

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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