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CASE SERIES

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First clinical case series of frosted branch angiitis: A diagnostic algorithm is suggested

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Key Clinical Message

FBA is a clinical diagnosis of a diverse spectrum, which needs a high index of suspicion to identify the possible specific etiologies. The zones of retinal involvement can help in predicting the final visual outcome. The proposed diagnostic algorithm facilitates meticulous evaluation and targeted treatment to improve the final visual outcome.

Abstract

Frosted branch angiitis is a clinical diagnosis of a diverse spectrum, which needs a high index of suspicion to identify the possible specific etiologies. We present a series of three cases of FBA with an attempt to formulate a diagnostic algorithm and refine the definition of FBA.

KEYWORDS

Behcet's, frosted branch angiitis, idiopathic, tuberculosis, uveitis

Work was carried out at: Aravind eye hospital and post graduate institute of Ophthalmology, Cuddalore main road, Thavalukuppam, Pondicherry, and Coimbatore India.

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1 | INTRODUCTION

Frosted Branch Angiitis (FBA) is an acute panuveitis with severe vasculitis affecting the entire retina. FBA was first described in 1976 in the Japanese literature by Ito in a 6-year-old child presenting with diffuse sheathing of all retinal vessels, producing the appearance of frosted branches of a tree.[1] As then it has been reported from North America, Turkey, Korea, Spain, Japan, and India. As there is a predilection for veins over arteries, it is also called as diffuse acute retinal periphlebitis.[2] It is typically bilateral with a higher male preponderance, although unilaterality (28%) does not rule out this entity.[1] The reported etiological categories of FBA are variegated, inconsistent and include *idiopathic, traumatic*, *infective* [cytomegalovirus (CMV), acquired immunodeficiency syndrome (AIDS) and toxoplasma, tuberculosis, familial Mediterranean fever, coagulase-negative staphylococci, streptococcus, herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), influenza type a, mycoplasma pneumoniae], *autoimmune* [systemic lupus erythematosus, Behcet's, Crohn's disease, antiphospholipid antibody syndrome (APLA), Wegner's granulomatosis, glomerulonephritis], *masquerades* [large cell lymphoma, acute lymphoblastic leukemia, Hodgkin's lymphoma], and *miscellaneous* [antithyroid medications, adalimumab, pediatric dyskeratosis congenita].[3]

Although a large number of cases have been documented, the initial published series of FBA are limited by the description of homogenous-specific etiologies and shorter duration of follow-up. The initial fundus fluorescein angiogram (FFA) definition of FBA[1] proposed a normal pattern in the first stage, with leakage of the dye from vessels in the later frames with emphasis on the sheathed vessels revealing no signs of occlusion. However, it is challenged by the recent findings of vascular occlusion in FBA, as several occlusive vasculitis like Behcet's disease can manifest with an FBA-like picture.[4] In addition, the previously published literature documents case reports and review articles on FBA, but none of them have described any case series with zones of involvement along with diagnostic algorithm. In this case series, we analyze the contemporary cases of FBA encompassing its heterogenous-specific etiologies with appropriate follow-up duration. We also attempt a plausible algorithm to the clinician for appropriate work-up and a treatment plan.

2 | CASE REPORT

2.1 | Case 1

A 47-year-old male presented with sudden onset, painless, defective vision in the right eye (RE) for past 3 days. Best corrected visual acuity (BCVA) was finger counting close to the face (FCF). Anterior segment examination revealed 1+ cells, 1+ flare, and relative afferent pupillary defect. Dilated fundoscopy revealed disc edema, telangiectatic vessels, and perivascular sheathing in all quadrants with all three zones of involvement. Optical coherence tomography (OCT) macula revealed a central macular thickness (CMT) of 565 μm. Fundus fluorescein angiography (FFA) depicted disc leakage with diffuse vascular leakage, and capillary non-perfusion areas throughout the retina. General examination revealed aphthous and genital ulcers. Blood investigations were normal except raised erythrocyte sedimentation rate. Corticosteroids were administered intravenously and periocularly, with the latter being through a posterior subtenon's injection. This was in addition to topical treatment with 1% prednisolone six times/day and 2% homatropine two times/day. A diagnosis of Behcet's disease was made by the rheumatologist. Due to a suboptimal response to steroids, intravenous cyclophosphamide and cyclosporine were commenced. The posttreatment visual acuity was 6/36 till 18 months of last follow-up (Figures 1, 2 and 3).

2.2 | Case 2

A 31-year-old male presented with sudden onset vision deterioration for four days. BCVA was 5/60 in both eyes (BE). Anterior segment examination revealed 1+cells. Fundus examination revealed disc edema, retinal edema, active vascular sheathing and subretinal fluid at macula along with Zone 2 and 3 involvement. OCT macula revealed CMT of 456 μm and 470 μm in RE and LE, respectively. FFA displayed mild disc staining with vascular staining and leakage in the superotemporal arcade. Blood investigations were normal. Patient was started on topical prednisolone and homatropine. A comprehensive evaluation done by an internist was inconclusive and the patient was labeled as a case of idiopathic FBA. The final BCVA was 6/6 till 15 months of follow-up (Figures 4, 5, and 6).

2.3 | Case 3

A 45-year-old female presented with sudden onset defective vision in RE for the past 2 days. The presenting BCVA was 3/60. Anterior segment examination revealed 1+cells in anterior chamber, and 1+ cells in the anterior vitreous face. Fundus examination showed vitreous membranes, hyperemic disc edema, retinal edema, sheathed vessels, and few choroidal folds with all three zones of involvement. OCT macula revealed a CMT of 440 μm. FFA showed disc staining, mild vascular staining along with leakage. Patient was started on topical 1% prednisolone

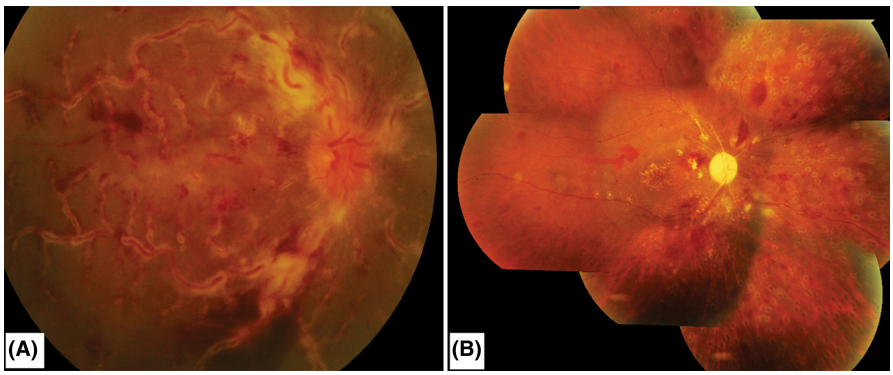
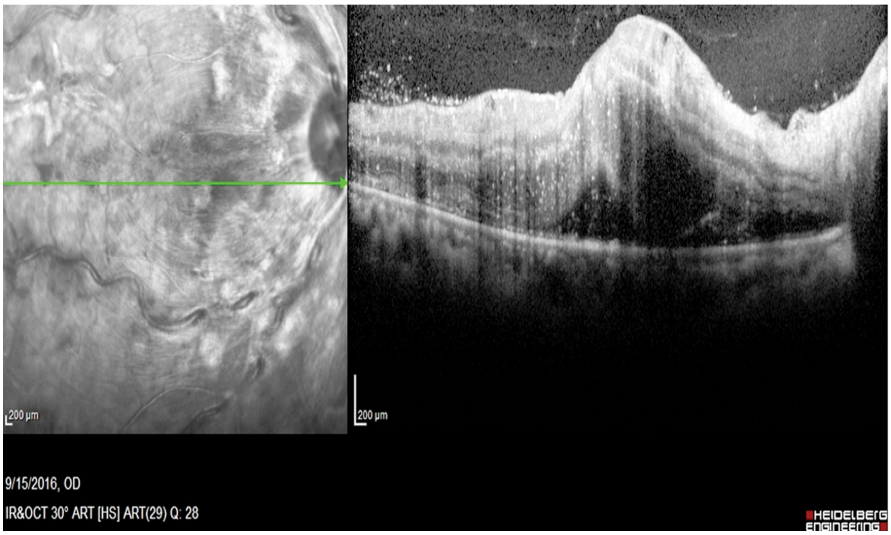


FIGURE 1 (A) Pretreatment fundus image of the right eye of the patient with FBA secondary to Behcet's disease depicting hyperemic disc with blurred disc margins, macular edema with a star, extensive perivascular sheathing with multiple flame-shaped hemorrhages, and cotton wool spots along the posterior pole with tortuous and dilated blood vessels. There is also a patch of intraretinal hemorrhage inferior to the inferotemporal arcade. (B) Posttreatment fundus montage of the patient's right eye depicting disc pallor with vascular sheathing along arcades and macular star. The nasal half of the retina shows chorioretinal atrophic patches due to laser marks along with intraretinal hemorrhage in all quadrants.

FIGURE 2 Optical coherence tomography (OCT) image of the macula of the right eye of the same patient hyperreflective irregular retinal layers suggestive of retinal edema with multiple hyperreflective dot echoes along with back shadowing suggestive of exudates and submacular fluid. They are dot echos in the posterior vitreous suggestive of vitreous hemorrhage.



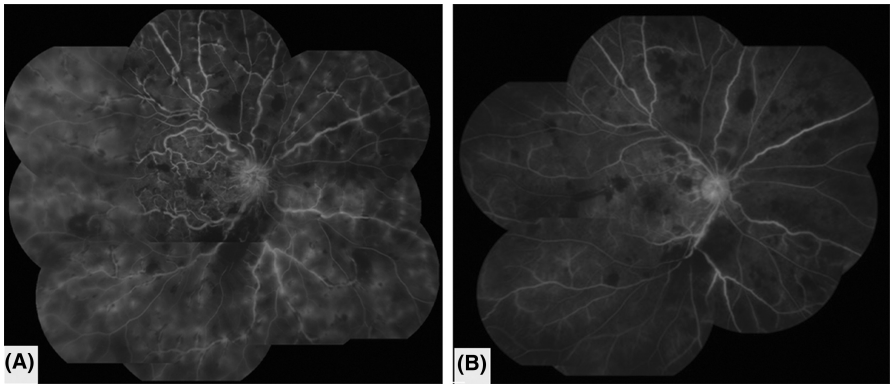


FIGURE 3 (A) Pretreatment late phase fundus fluorescein angiography (FFA) montage of the right eye of the same patient depicting disc leakage, irregular foveal avascular zone, tortuous blood vessels with vascular leakage and diffuse staining, capillary non-perfusion areas throughout the retina. There are also multiple hypo fluorescent patches at the posterior pole due to blocked choroidal fluorescence. (B) Posttreatment late phase fundus fluorescein angiography (FFA) montage of the right eye of the same patient depicting reduced disc leakage, mild staining of blood vessels, irregular foveal avascular zone, and blocked choroidal fluorescence.

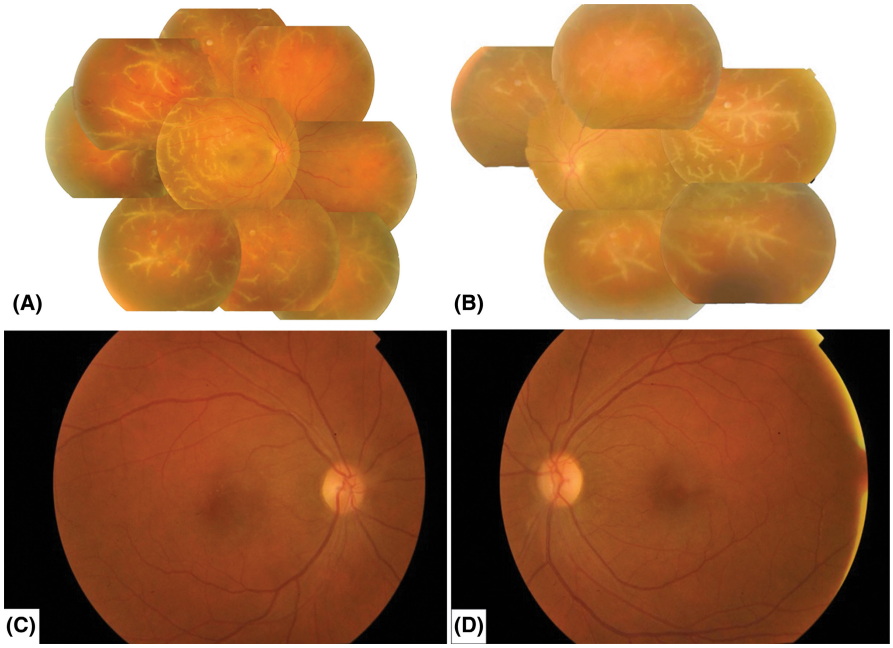


FIGURE 4 (A, B) Pretreatment fundus montage image of the right eye and left eye of the patient with idiopathic FBA depicting disc edema with hyperemia, and macular edema, tortuous dilated blood vessels, perivenous cuffing, and scattered intraretinal hemorrhages. (C, D) Posttreatment normal fundus image of the right and left eye.

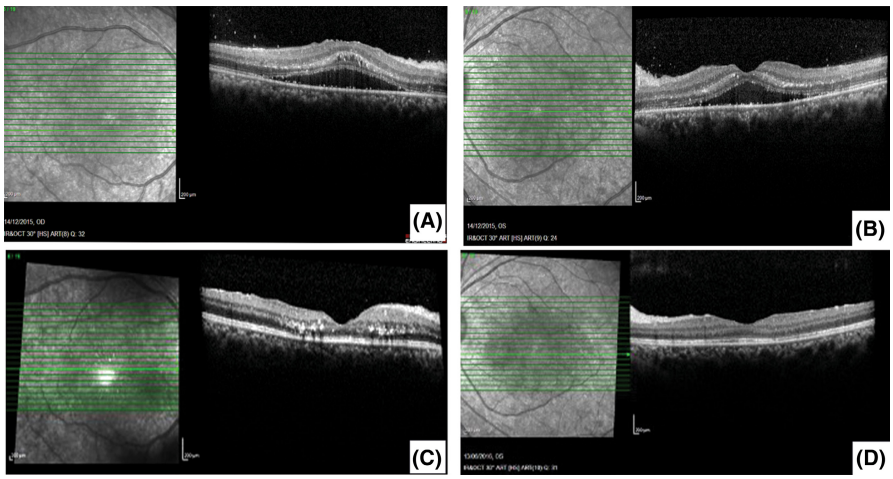


FIGURE 5 (A, B) Pretreatment optical coherence tomography (OCT) image of the macula of both eyes of the same patient depicting multiple hyperreflective dot echo's in all retinal layers. (C, D) Posttreatment normal OCT of both the eyes.

drops four times/day. Blood investigations were normal, except for a positive Mantoux with 15 mm induration. Patient was referred to an internist, where chest x-ray imaging revealed bilateral hilar lymphadenopathy, and quantitative polymerase chain reaction of vitreous was positive for mycobacterium tuberculosis antigens MPB64. Patient was started on antitubercular therapy (ATT) and oral steroids. The final visual acuity improved to 6/36 till 12 months of last follow-up (Figure 7). A summary of all three cases in listed in Table 1.

3 | DISCUSSION

FBA is a descriptive term for a unique type of posterior uveitis and widespread retinal vasculitis.[1] The florid translucent perivascular exudate inspired the descriptive term "Frosted Branch Angiitis."[3] FBA predominantly affects the young and healthy. The youngest patient reported to date was 2 years and the oldest 48 years. The most common presenting symptoms include subacute visual loss, floaters, and photopsia. Visual acuity can be substantially reduced to the extent of perception of light.[5] Most patients (75%) have bilateral affliction. There have been few reports of FBA from India in the recent past, where the etiology or association has been idiopathic, trauma, cytomegalovirus (CMV), AIDS, tuberculosis, glomerulonephritis, typhoid fever, sympathetic ophthalmia, endophthalmitis, central retinal vein occlusion, vitreous hemorrhage, and pregnancy. The specific diagnostic criterion were used for tuberculosis[6] and Behcet's disease.[7] Table 2 outlines a comprehensive comparative analysis of the published cases in the literature.[8–13]

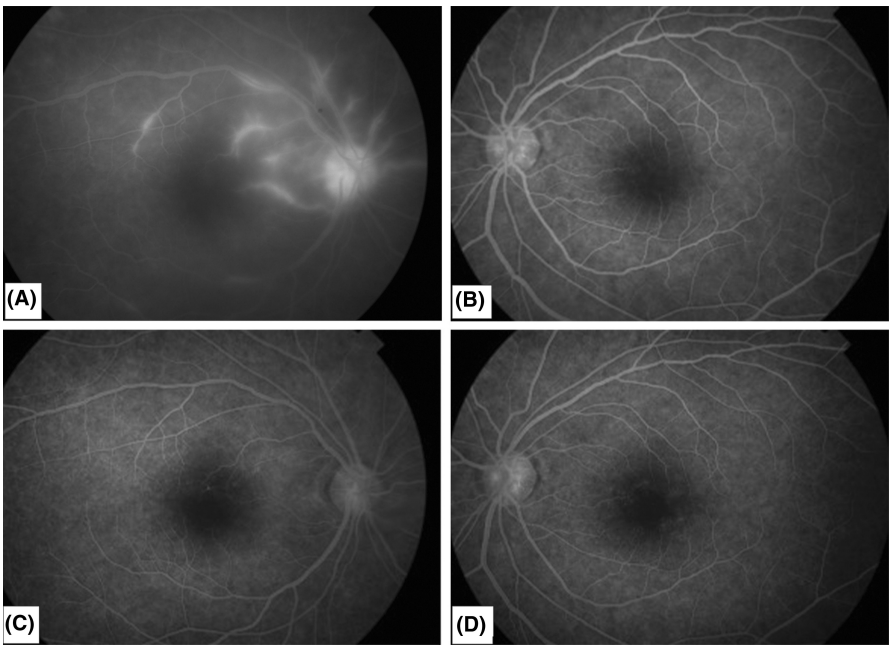


FIGURE 6 (A) Pretreatment fundus fluorescein angiography (FFA) image of the right eye of the same patient depicting disc staining with mild vascular staining and leakage along the supero-temporal arcade. (B) Pretreatment normal FFA image of the left eye of the patient. (C, D) Posttreatment normal FFA image of both eyes of the patient.

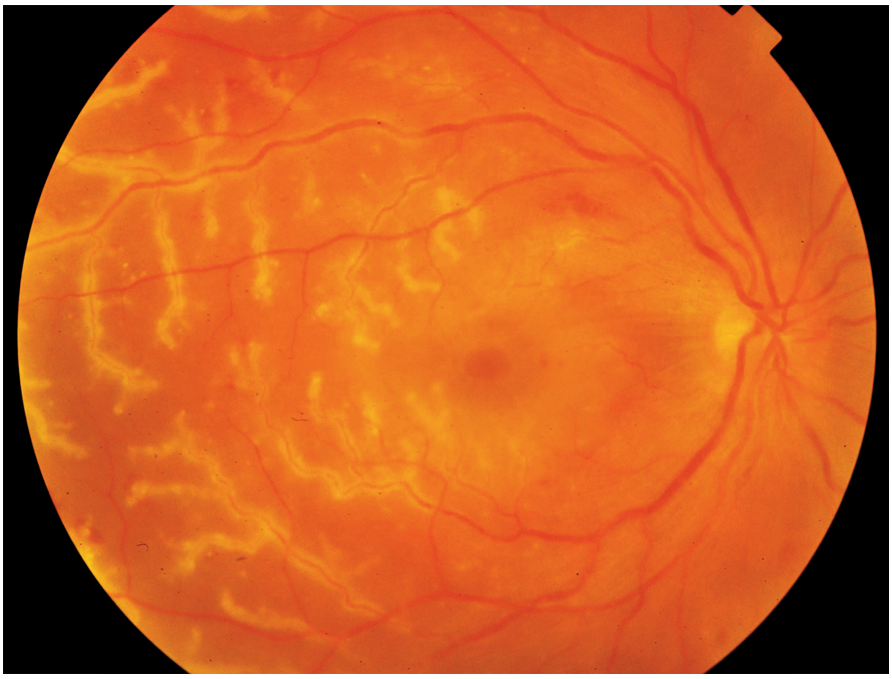


FIGURE 7 Fundus image of the patient with tubercular etiology depicting severe sheathing of retinal vessels along with macular edema.

Kleiner et al.[2] classified FBA into three distinct subgroups (Table 2 and Figure 8). The pathogenesis of FBA can be broadly categorized as idiopathic and non-idiopathic. The former encompasses those cases where the etiology largely remains unknown. The prompt response to steroids in such cases also suggests a probable immune-mediated mechanism. Non-idiopathic includes those patients with associated viral diseases (EBV, Rubella, CMV, AIDS), where it has been postulated that viral antigens form immune complexes and deposit in retinal vessels causing vasculitis. A direct viral injury to endothelial cells (CMV has a particular tropism for endothelial cells) has also been held responsible for the pathogenesis.

The treatment of FBA in the immunocompetent group includes corticosteroid after excluding the treatable specific causes. In non-resolving cases, long-term immunosuppression and additional use of biologicals can be beneficial to prevent recurrence.[14] The prognosis in FBA is usually good. Although complications are rare, they include neovascular glaucoma, macular scarring, retinal detachments, and vitreous hemorrhage in untreated cases.

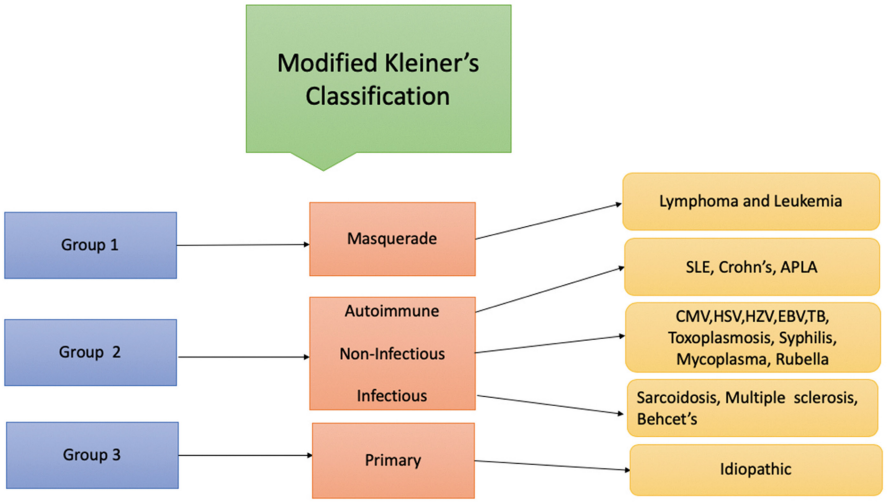
TABLE 1 Clinical profile of various etiologies of frosted branch angiitis.

Case No	Etiology age	Eye	Visual acuity (V.A.)	Anterior segment findings	Fundoscopy	Key investigations and management	Diagnostic clues	Zones of involvement[12]	Follow-up, response, and final VA
1	Behcet's 47 years	RE	FCF	1+ cells, flare, Relative afferent pupillary defect	Perivascular sheathing, telangiectatic vessels, disc edema (Figure 1)	Blood investigations-normal, raised ESR OCT macula- CMT 565 um FFA- Image 3a and 3b steroids, cycloplegics, cyclophosphamide and cyclosporine	Aphthous and genital ulcers, diagnosed by rheumatologist. Had suboptimal response to steroids alone and improved with cyclosporine	1,2,3	18 months, improved with immuno suppressants Posttreatment visual acuity 6/36
2	Tuberculosis 45 years	RE	3/60	Normal	1+ Anterior vitreous phase (AVF) cells, Vitreous membranes, Sheathed vessels, few choroidal folds, and retinal edema	OCT macula-CMT 440 um FFA-Perivascular leakage with disc leakage Anti-tubercular therapy (ATT) and oral steroids in tapering doses	Mantoux-15 mm induration, Chest imaging showed bilateral hilar lymphadenopathy, Qualitative polymerase chain reaction (PCR) of vitreous was positive for mycobacterium tuberculosis antigens [MPB64, IS6110] Poor response to oral steroids alone, Prompt response to ATT + oral steroids	1,2,3	12 months, improved with ATT and steroids, posttreatment visual acuity 6/36
3	Idiopathic 31 years	BE	5/60	1+ cells	Active vascular sheathing, retinal edema, subretinal fluid at macula (Figure 2)	Blood investigations-normal OCT macula-CMT-456 um O.D. and 470um OS FFA-Image 6a and 6b steroids and cycloplegics	Color vision defect present, Visual fields show peripheral constriction	2, 3	15 Months, improved with steroids, posttreatment visual acuity 6/6

TABLE 2 Modified Kleiner's classification.

S. No	Group	Category	Pathology
1	Group 1	Masquerade	Lymphoma Leukemia
2	Group2	Autoimmune	Systemic lupus erythematosus. Chron's disease, Anti-phospholipid antibody syndrome.
		Non-Infectious	Sarcoidosis, multiple sclerosis, Behcet's disease.
		Infectious	Cytomegalovirus, herpes simplex virus, herpes zoster virus, Epstein–Bar virus, tuberculosis, toxoplasmosis, syphilis, mycoplasma, rubella.
3	Group 3	Primary	Idiopathic

FIGURE 8 Image depicting Kleiner's classification.



The first case with Behcet's disease had profoundly low BCVA of FCF at presentation. The patient showed a prompt response to cyclosporine, eventually attaining a BCVA of 6/36 at 18 months of follow-up. Kwon et al.[15] reported a case of a 39-year-old male with unilateral FBA associated with Behcet's disease treated with systemic steroids and cyclosporine. They showed that early initiation of cyclosporine is crucial in treating FBA secondary to Behcet's disease. Our case is consistent with the same.

The second patient was diagnosed with idiopathic FBA having a BCVA of 5/60 in BE. The patient showed a good response with steroids with a final BCVA of 6/6. Consistent with our case, a good response with steroids was reported by Maleki et al.[16] in a case of idiopathic bilateral FBA in a 5-year-old child with a BCVA of hand motion in BE. Fundus examination revealed prominent and florid retinal perivascular infiltration with predominant affliction of venules, initiating from the posterior pole and extending up till the periphery. The child showed resolution with empirical treatment using oral prednisolone (1 mg/kg/day) and topical corticosteroids resulting in a final BCVA of 6/20 in BE.

The last patient with tuberculosis presented with a BCVA of 3/60 in LE. Due to a history of contact with tuberculosis and poor response to oral steroids initiated elsewhere, PCR for MPB 64 primer was contemplated and was conclusive of tuberculosis. The patient showed a good therapeutic response with ATT and steroids with a final BCVA of 6/36. Zhao et al.[6] reported a case of a 27-year-old woman of tuberculous meningitis with sheathing of the retinal venules and arterioles, consistent with FBA in BE. After treatment with ATT and steroids, FBA resolved. In endemic countries, the clinical clue to tuberculosis could arise from poor response to oral steroids, a positive response to the addition of ATT, and consistent PCR reports.

FBA may affect any part of the retina and impact the visual potential. In our case series, all three patients had low presenting BCVA ranging from FCF-5/60, which is consistent with previously published reports. Moreover, all patients had a final BCVA ranging from 6/36 to 6/6, which confirms a good response of FBA to focused specific treatment. All three zones were involved in the two patients with Behcet's disease and tuberculosis. This can

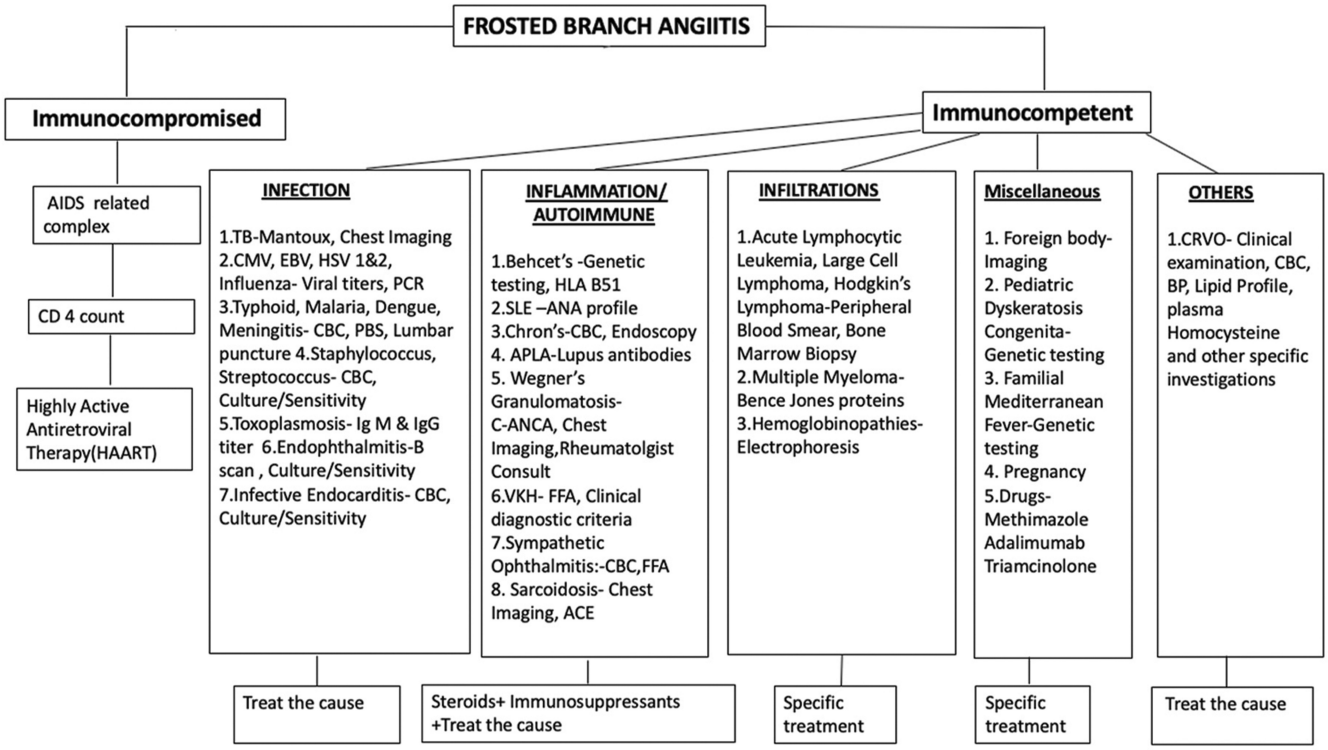


FIGURE 9 Flowchart for diagnosis for FBA.

be corroborated with reduced presenting BCVA and macular involvement. Zones 2 and 3 were involved in the patient with idiopathic FBA and can be very well correlated with the final BCVA of 6/6 in this variant.

The limitations of this case series include the retrospective nature of the case series and the small sample size of this specific entity. The evaluation done in cases is tailored individually based on the clinical scenario and not homogenously in all the patients. The electrophysiological tests could not be done in them due to feasibility and financial constraints. Beyond immunosuppressants, biologicals could not be initiated in the case of Behcet's associated FBA due to financial constraints.

After an extensive literature search and to the best of our knowledge, this is the first-ever case series of FBA with specific documentation of the zones of involvement.[17] In particular, we attempted to formulate a diagnostic algorithm for the meticulous evaluation of FBA in a clinical scenario (Illustrated in Flowchart: Figure 9). This is a practical suggestion that merits being validated by future studies. Hence FBA is a clinical diagnosis of a diverse spectrum, which needs a high index of suspicion to identify the possible specific etiologies. Meticulous examination, close follow-up, and tailored treatment are necessary for treatment success. We would like to refine the definition of FBA as a unique type of retinal vasculitis with a specific frosted branch configuration proven angiographically to reveal findings with or without occlusion and chorioretinal lesions. Table 3 depicts the review of literature of few important cases of FBA. Table 4 depicts the investigations required to rule out the etiology of FBA.

3.1 | Pointers for Future Research in Frosted Branch Angiitis

The exact antigens involved in eliciting this peculiar frosted branch configuration, the dynamic interplay of the varied innate, complement, and cellular immune systems with advanced molecular studies and imaging modalities using stable isotope labelling metabolomics, might shed additional insights to discern the pathogenesis of this distinct disease. It shall translate into targeted medical treatment and unravel the enigma of this heterogenous disease spectrum. There is also a need to compare FBA with or without capillary non-perfusion areas and look for the predictors of good and poor outcomes with sufficiently larger sample size. There is also a felt need for large-scale studies with specific diagnostic markers for the specific etiologies that shall facilitate the clinicians to pinpoint the etiologies of FBA elegantly.

TABLE 3 Review of literature of frosted branch angiitis.

Published data	Chan et al.[8] Ophthalmol Retina Dec 2018	Wood et al.[9] J Ophthalmic Inflamm Infect Dec 2016	Kim et al.[10] KJO Oct 2019	Moustafa et al.[11] Clin Case Rep Aug 2018	Agarwal et al.[12] Ocul Immunol Inflamma 2018	Annamalai et al.[12] Oman J Ophthalmol Jan–Apr 2018	Our case series
Etiology	Familial mediterranean fever	Antiphospholipid antibody syndrome	Wegner's granulomatosis	Hodgkins lymphoma	Typhoid fever	Sympathetic ophthalmia	Heterogenous seven patients 1-Tuberculosis 1-Idiopathic 1-Behcet's
Laterality	LE	BE	LE	BE	LE	RE	4 eyes, 1 B/L 2 U/L
Age (years)	47	28	70	71	16	25	31–47
Presenting visual acuity	20/70	FCF RE 20/40 LE	Finger counting at 30 cm	20/30 RE 20/50 LE	LE 6/18	RE 6/9	FCF-5/60
Risk factor	Fever		Acute kidney injury hemodialysis	Stage IIa classical H.L.	Typhoid fever	Trauma	Immunosuppression
Anterior segment	-	An afferent pupillary defect was noted RE, 1+ anterior chamber cell on the right with no anterior chamber cell on the left.	Mild anterior uveitis	-	Anterior chamber cells and flare 2+ with vitreous cells 2+	Mutton-fat keratic precipitates and aqueous cells1+and aqueous flare 1+.	Anterior uveitis all three patients with cells and flare, one had RAPD
Posterior segment	Perivenular sheathing and hemorrhages	2+ bilateral vitritis, bilateral diffuse retinal periphlebitis resembling frosted branch angiitis	Extensive perivascular sheathing, multiple retinal hemorrhages	Frosted branch pattern periphlebitis.	Mild vitreous haze, disc hyperemia, and extensive perivascular sheathing involving arterioles and venules in all the quadrants with an appearance characterized as "frosted branch angiitis"	1+ vitreous haze and disc hyperemia with multiple Dalen-Fuchs nodules, perivascular retinitis, and extensive vascular sheathing.	All had FBA like picture
Investigation	MEFV V726A mutation FFA OCT	FFA OCT Blood tests anti-nuclear antibody	C-ANCA Renal biopsy FFA OCT	FFA CT Chest, abdomen, and pelvis PET scan	Blood tests FFA OCT PCR	FFA OCT USG B Scan	Tailored to specific etiologies
Treatment	Oral prednisone, Colchicine	Oral prednisone, at 1.5 mg/kg/day.	IV Prednisolone 1 g/day for 3 days Oral cyclo phosphamide (100 mg/day)	IV brentuximab vedotin and intraocular injections of bevacizumab1.25 mg/0.05 mL monthly for 4 months	Oral prednisolone 60 mg/day (1 mg/kg per day)	Oral azathioprine 50 mg three times daily and tablet prednisolone 60 mg along with antacid and calcium supplements.	Topical and oral steroids, Cyclosporine-Behcet's ATT-Tuberculosis Steroids- Idiopathic
Follow-up	1 month	4 months	6 months	6 months	3 months	1 year	Minimum 1 year
Final visual acuity	20/30	20/20	6/15	20/25 RE 20/65 LE	6/6	6/6	6/36–6/6
Remarks	No recurrences after use of colchicine	Criteria for diagnosis for APLA fulfilled but not SLE	IV Dexamethasone implant 2 months later for macular edema	Posttreatment-subfoveal choroidal neovascular membrane	Treatment for enteric fever	Tablet cyclosporine, 150 mg twice daily, was added to the treatment.	Heterogenous etiologies, first case series on FBA, use of zones of involvement

TABLE 4 Depicts the investigation necessitated for diagnosing etiology of frosted branch angiitis.

S. No	Classification	FBA etiology	Investigations required
1	Infection	Acquired immunodeficiency syndrome (AIDS)	CD 4 count, CD 8 count, CD4/CD8 ratio
		Tuberculosis	Mantoux, Chest Imaging, QuantiFERON Gold TB assay
		Cytomegalovirus, Epstein–Bar virus	Viral IgG and IgM titers
		Herpes simplex virus 1 and 2	Polymerase chain reaction
		Influenza	
		Typhoid	Complete blood count (CBC), Widal test
		Malaria	CBC, Peripheral blood smear
		Dengue	CBC, Platelet count (specific)
		Meningitis	CBC, Lumbar puncture
		Staphylococcus, streptococcus	CBC, Culture and sensitivity
		Toxoplasma	CBC, IgG and IgM titers
		Infective endocarditis	CBC, Culture and sensitivity
		Endophthalmitis	B scan, Vitreous tap, biopsy and culture and sensitivity
2	Autoimmune/ inflammation	Behcet's disease	Genetic workup, HLA B51
		Systemic lupus erythematosus	Antinuclear antibody (ANA) titer
		Chron's disease	CBC, CECT, Endoscopy
		Antiphospholipid antibody syndrome	Lupus antibodies
		Wegner's granulomatosis	C-ANCA, Chest IMAGING
		Vogt-Koyanagi-Harada syndrome	Fundus fluorescein angiography (FFA)
		Sympathetic ophthalmia	CBC, FFA
		Sarcoidosis	Chest imaging, angiotensin converting enzyme (ACE) levels
3	Infiltration	Acute lymphocytic leukemia, large cell lymphoma, Hodgkin's lymphoma	Peripheral blood smear, bone marrow biopsy
		Multiple myeloma	Bence Jones proteins
		Hemoglobinopathies	Electrophoresis
4	Miscellaneous	Foreign body	Imaging
		Pediatric dyskeratosis congenita	Genetic testing
		Familial Mediterranean testing	Genetic testing
		Pregnancy	Specific tests related to trimester
5	Others	Central retinal vein occlusion	CBC, blood pressure, lipid profile, plasma homocysteine levels

AUTHOR CONTRIBUTIONS

Bharat Gurnani: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Sivaraman Balamurugan:** Conceptualization; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization. **Anuradha Kanakath:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft. **Kirandeep Kaur:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Abhay Gupta:** Data curation; investigation; methodology; visualization; writing – review and editing. **Sameer Chaudhary:** Investigation; methodology; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The patient details are available in the electronic medical records and can be made available from the authors on request.

ETHICS STATEMENT

At our institute case reports, images and case series are exempted from IRB approval and the research followed the tenets of the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from all the patients to publish this case series in accordance with the journal's patient consent policy.

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