Sarcoidosis

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Introduction

Sarcoidosis is a chronic inflammatory disease of unknown etiology characterized by the formation of noncaseating epithelioid granuloma in multiple systemic organs such as lung, lymph nodes, eyes, or skin. The other organs including heart, liver, bones, salivary glands, nervous, or muscles are also affected but the incidences are much less. Among all sarcoidosis patients, about 40–50% of the patients develop ocular complications including granulomatous uveitis (Obenauf et al. 1978; Jabs and Johns 1986; Ohara et al. 1992). The ocular symptoms such as photophobia, blurred vision, or floaters, often appear as the first symptoms of sarcoidosis. Although the etiology of sarcoidosis is not known yet, systemic cellular immune responses against certain microbes such as *Mycobacterium tuberculosis* (Fang et al. 2016), *Propionibacterium acnes* (Ishige et al. 2005; Negi et al. 2012), or *mumps virus* (Uzun et al. 2004) are hypothesized to be the causative antigen to form granulomas in sarcoidosis. Most frequently affected ages by sarcoidosis distribute between the third to fifth decade of life in both genders, and elderly women are also affected (Silver and Messner 1994). Sarcoidosis is currently the most frequent cause of uveitis in Japan (Ohguro et al. 2012), but it is not the case in other countries including neighboring Asian countries. In general, African American, Asian, and South Americans are often affected by sarcoidosis, while Caucasian people are less affected.

The gold standard to diagnose sarcoidosis is histopathological proof of noncaseating epithelioid granuloma, but biopsy is essentially not possible to perform using intraocular tissues, and biopsy in other organs could not easily be done because it is invasive procedure especially for the patients who do not have systemic symptoms other than the eye. Therefore, diagnosis of sarcoidosis is usually performed based on a combination of clinical intraocular signs and systemic investigational tests. In 2006, the first international workshop on ocular sarcoidosis (IWOS) was held, and the international diagnostic criteria for ocular sarcoidosis (IWOS criteria) were established (Herbort et al. 2009). These criteria were revised in 2017, but the intraocular clinical signs included in both criteria are identical as described in the next section.

Clinical Features

The intraocular clinical features suggestive of sarcoidosis described in IWOS criteria are: mutton fat keratic precipitates and/or iris nodules at the pupillary margin (Koeppe) or in the stroma (Busacca), trabecular meshwork nodules and/or tent-shaped peripheral anterior synechia, snowball/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions (active and atrophic), nodular and/or segmental periphlebitis and/or macroaneurysm in an inflamed eye, optic disc nodule/granuloma and/or solitary choroidal nodule, and bilaterality assessed by clinical examination showing subclinical inflammation (Herbort et al. 2009) (Table 11.1). The granulomatous signs in the anterior segment can easily be diminished by local steroid therapy, so it is very important to actively look

Table 11.1 Clinical signs suggestive of ocular sarcoidosis by IWOS criteria (Herbort et al. 2009)

1.	Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca)
2.	Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3.	Snowballs/string of pearls vitreous opacities
4.	Multiple chorioretinal peripheral lesions (active and atrophic)
5.	Nodular and/or segmental periphlebitis (± candlewax drippings) and/or macroaneurysm in an inflamed eye
6.	Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7.	Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

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for the signs of granuloma in every tissue of the eye before initiating steroid treatment using slit lamp biomicroscopy, gonioscopy, indirect fundoscopy, and other imaging tools such as fluorescein or indocyanine green angiography (FA, ICGA) or optical coherence tomography (OCT).

Retinal and Choroidal Involvements

Multiple chorioretinal lesions are regarded to be the sign of retinal or choroidal granuloma which appears to be yellowish-white lesions in its active phase. The lesions in the shallow layer of the retina look similar to the scars of laser photo coagulation in its atrophic phase (Fig. 11.1). Only a few chorioretinal lesions sometimes appear (Fig. 11.2a), while a number of lesions are sometimes observed in a close formation (Fig. 11.2b).

Retinal lesions also appear as yellowish subretinal exudative lesions (Fig. 11.3), and FA shows mottled hyperfluorescence in the corresponding area (Fig. 11.4). Although the other area of the retina looks normal, FA sometimes shows extensive hyperfluorescence in the retina or the retinal veins.

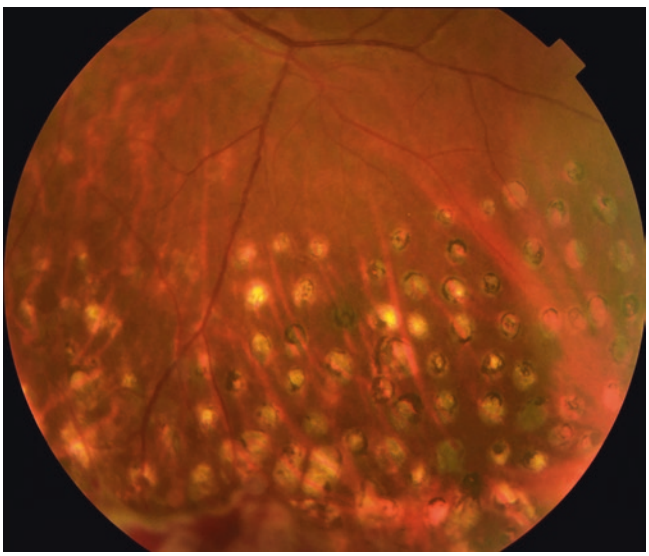

Fig. 11.1 Chorioretinal lesions composed of fresh yellowish-white lesions and atrophic laser-scar like lesions in the peripheral retina

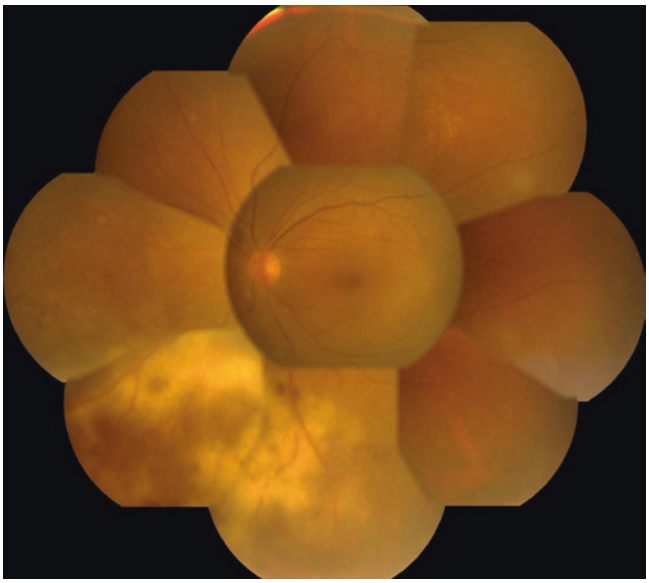

Fig. 11.3 Subretinal yellowish exudative lesions in the nasal-inferior part of the retina

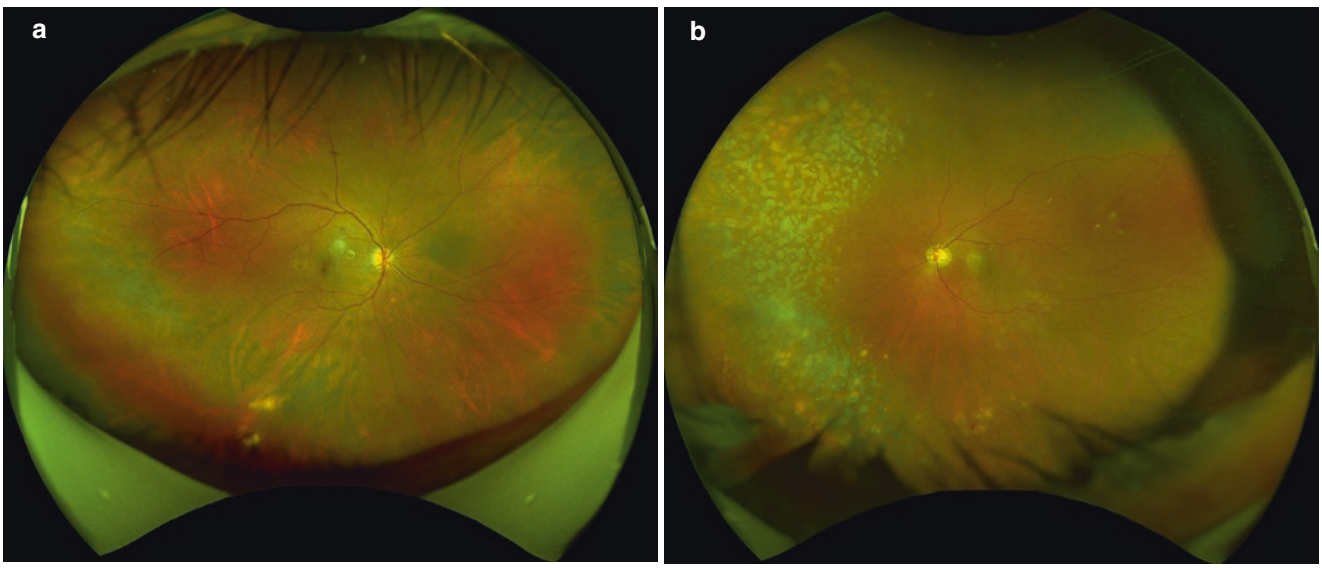

Fig. 11.2 (**a**) A few yellowish-white chorioretinal lesions are seen in the inferior part of the retina. (**b**) A number of chorioretinal lesions seen in close formation in the nasal part of the retina

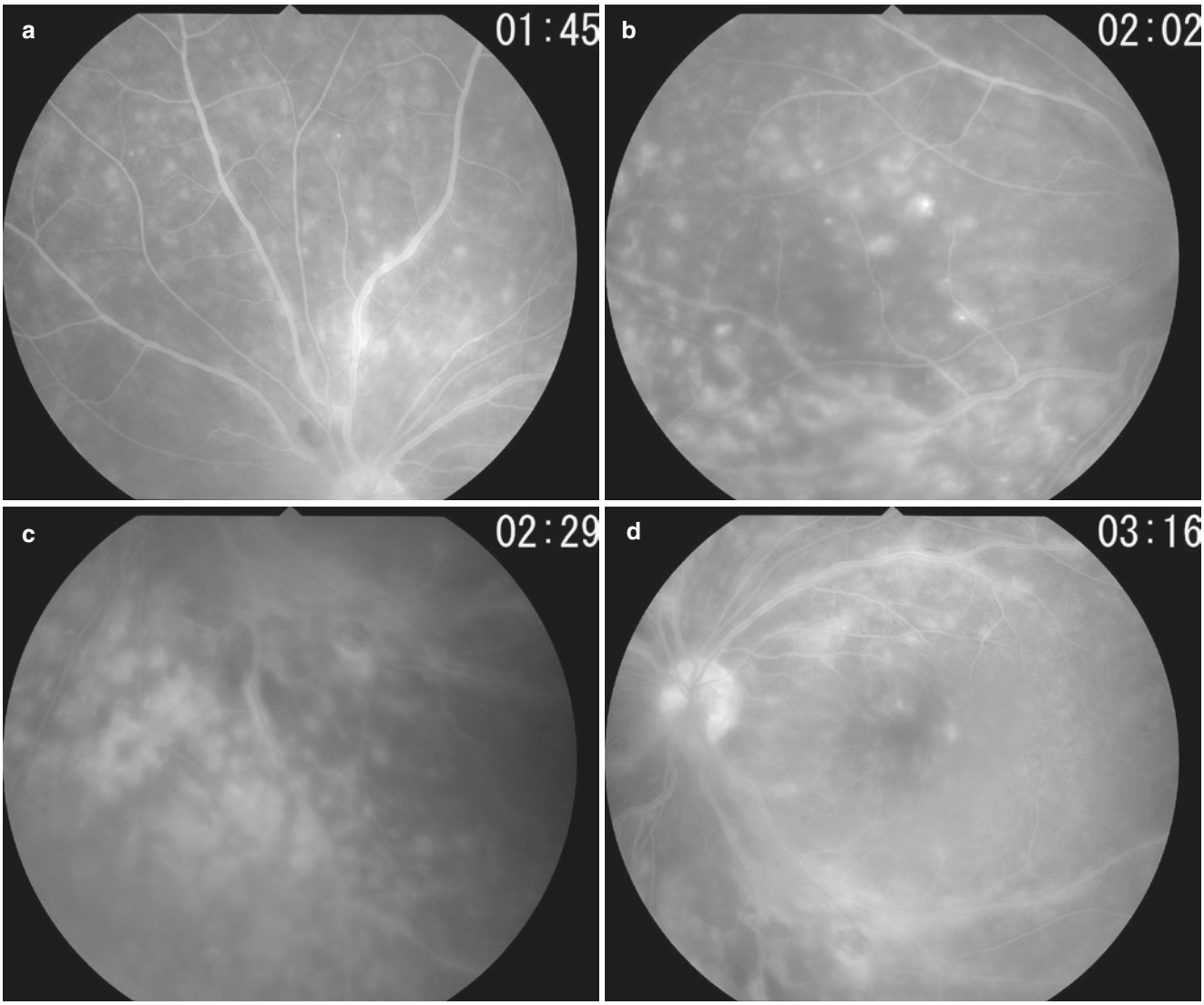

Fig. 11.4 Fluorescein angiography (FA) shows mottled hyperfluorescence corresponding to the subretinal exudative lesions (**a**–**d**). Although the other area of the retina looks basically normal in the color fundus photo (Fig. 11.3), FA shows small patchy hyperfluorescence in the whole fundus and segmental hyperfluorescence in the retinal vein

The chorioretinal lesions can present in the deeper layer of the retina or in the choroid (Fig. 11.5a). While FA does not detect such lesions, ICGA can show the presence of the chorioretinal lesions in the deeper layers as multiple hypofluorescence dots (Fig. 11.5b, c).

Choroidal granuloma is a rare form of intraocular sign of sarcoidosis. It is observed as subretinal yellowish lesion with dull margin (Fig. 11.6a). Ultrasound imaging shows the elevated lesion (Fig. 11.6b), and OCT shows the thickened choroid and elevated RPE (Fig. 11.6c). OCT also detects the subretinal infiltrates, and this may be shown as hyperfluorescein area by FA (Fig. 11.6d). ICGA shows broadly distributed dark spots, and choroidal folds surrounding the granuloma (Fig. 11.6e). Optic disc nodule also is a rare form of intraocular sign of sarcoidosis (Fig. 11.7). The specificity of choroidal granuloma and optic disc nodule is high in patients with sarcoidosis when compared to other types of uveitis (Takase et al. 2010; Acharya et al. 2018). Choroidal granuloma eventually causes chorioretinal atrophy and retinal pigment epithelium degeneration (Figs. 11.8 and 11.9).

Retinal Vascular Involvements

Sarcoidosis affects retinal veins as perivascular exudates, so-called candle-wax drippings, along with the retinal vein (Fig. 11.10a), or segmental nodular periphlebitis along with the retinal vein (Fig. 11.11a). FA shows diffuse hyperfluorescence in the perivascular exudates (Fig. 11.10b), while FA shows segmental hyperfluorescence in the nodular periphle-

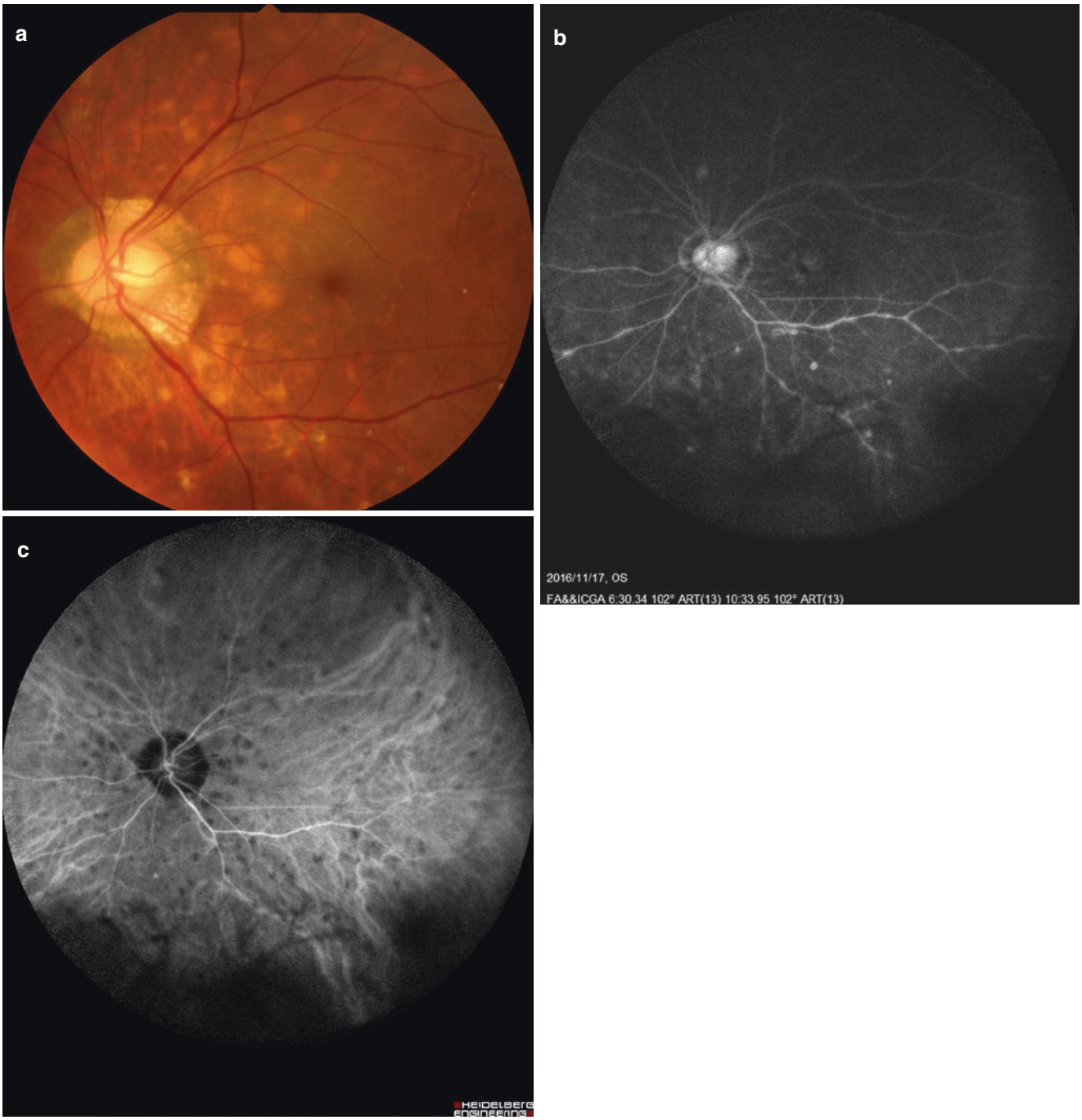

Fig. 11.5 (**a**) The chorioretinal lesions in the deeper layer of the retina or in the choroid are seen in the posterior pole. (**b**) Fluorescein angiography does not detect the chorioretinal lesions in the deep layer of the retina or in the choroid, but show some hyperfluorescein dots corresponding to the chorioretinal lesions in the shallow layer of the retina. Segmental hyperfluorescein are seen in the temporal-inferior retinal vein. (**c**) Indocyanine green angiography can show the presence of the chorioretinal lesions in the deeper layers as multiple hypofluorescence dots

bitis (Fig. 11.11b). Severe sheath formation of the retinal vein can also be seen although it is relatively rare (Fig. 11.12a). Fluorescein angiography shows diffuse hyperfluorescence in the corresponding retinal vein (Fig. 11.12b). Even when retinal periphlebitis is absent or just faint nodular periphlebitis is seen, FA sometimes shows nodular hyperfluorescence more than expected from the appearance of the fundus (Fig. 11.13). As for retinal artery involvement, macroaneurysm accompanied with intraocular inflammation is sometimes seen (Fig. 11.14).

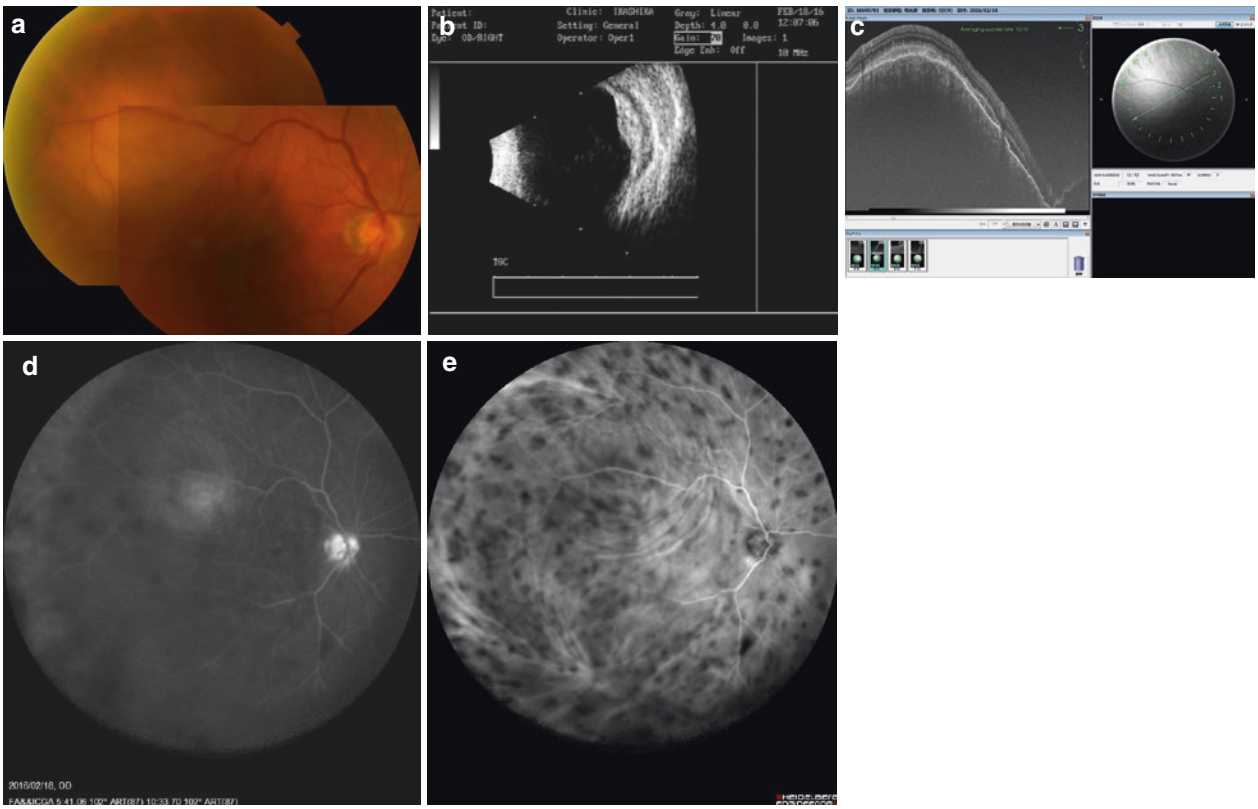

Fig. 11.6 (**a**) Choroidal granuloma is observed as subretinal yellowish lesion with dull margin. (**b**) Ultrasound imaging shows the elevated lesion corresponding to the choroidal granuloma. (**c**) Optical coherence tomography shows the thickened choroid, elevated RPE corresponding to the choroidal granuloma, and subretinal infiltrates. (**d**) The area of subretinal infiltrates corresponding to the choroidal granuloma is shown as hyperfluorescein area by fluorescein angiography. (**e**) Indocyanine green angiography shows broadly distributed dark spots, and choroidal folds surrounding the granuloma

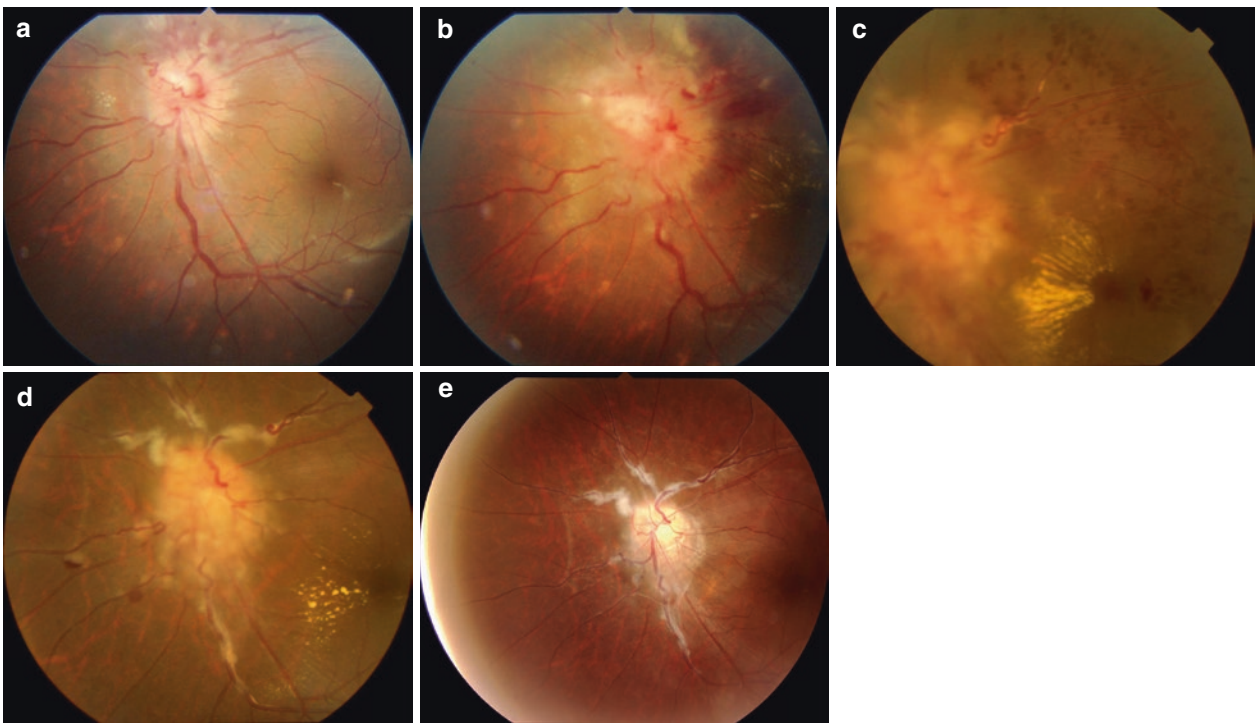

Fig. 11.7 Serial color photos of the optic papillitis from its occurrence (**a**) to remission (**e**). Following the inferior retinal vasculitis (**a**), optic disc edema (**b**) and multiple nodules occurred (**c**). After steroid pulse therapy and oral prednisolone, the optic edema improved (**d**), and the nodules disappeared (**e**)

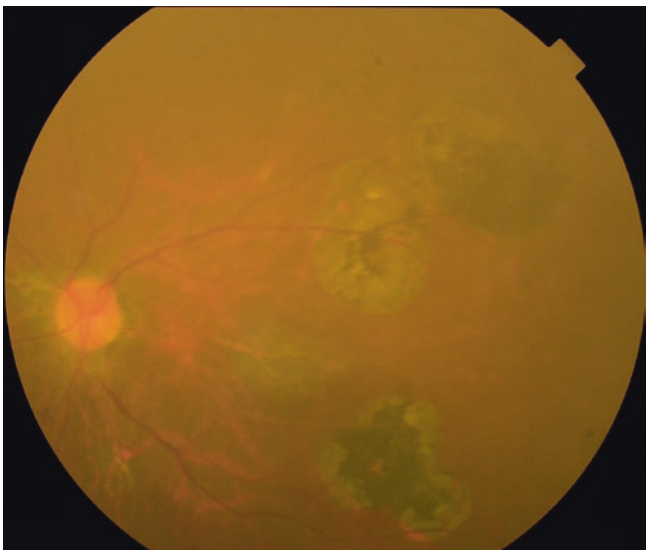

Fig. 11.8 Patchy subretinal atrophic lesions and retinal pigment epithelium degenerations are seen in the nasal part of the retina

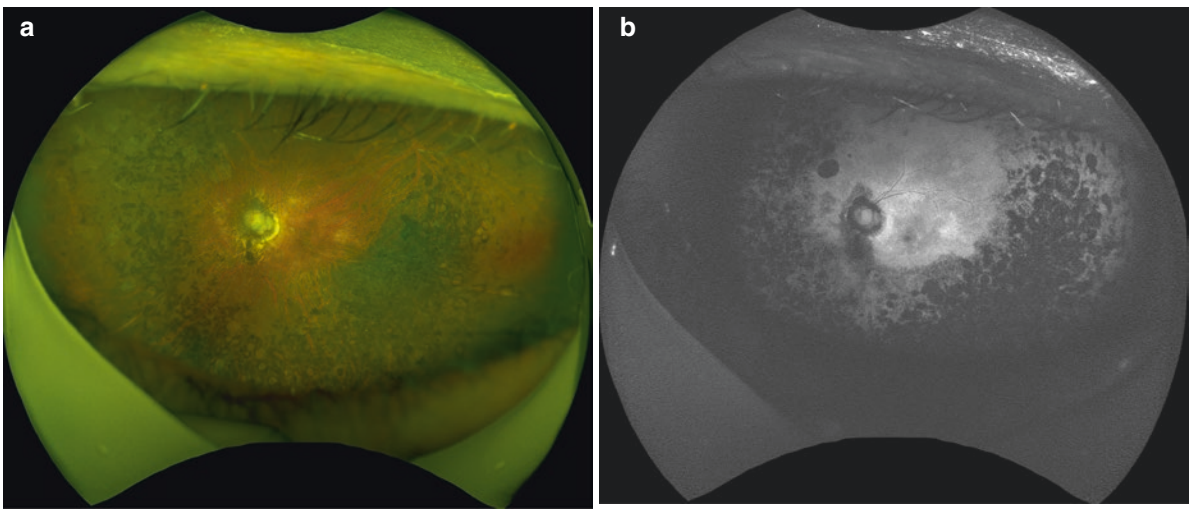

Fig. 11.9 (**a**) Broadly distributed chorioretinal degenerations as well as retinal pigment epithelium (RPE) degenerations are observed. (**b**) Fundus autofluorescence shows the degenerative RPE as mottled hypoautofluorescence area

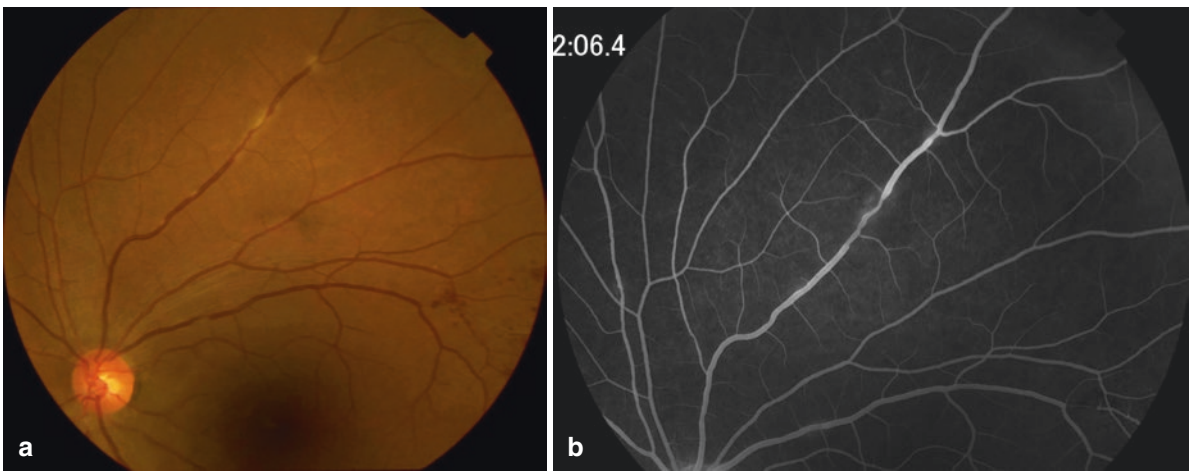

Fig. 11.10 (**a**) Perivascular exudates, so-called candle-wax drippings, are seen along with the retinal vein. (**b**) Fluorescein angiography shows diffuse hyperfluorescence in the corresponding area

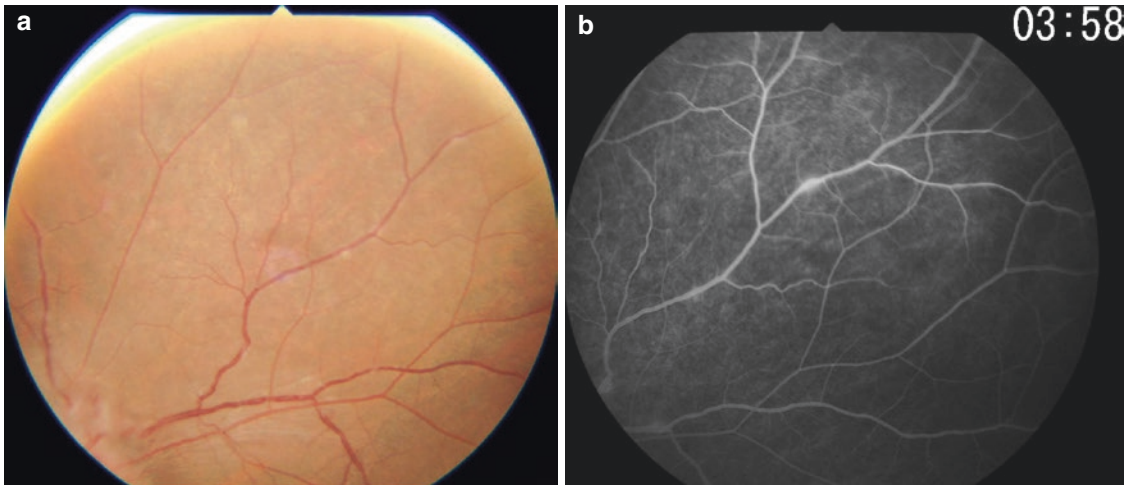

Fig. 11.11 (**a**) Nodular periphlebitis are seen along with the retinal vein. (**b**) Fluorescein angiography shows segmental hyperfluorescence in the corresponding area

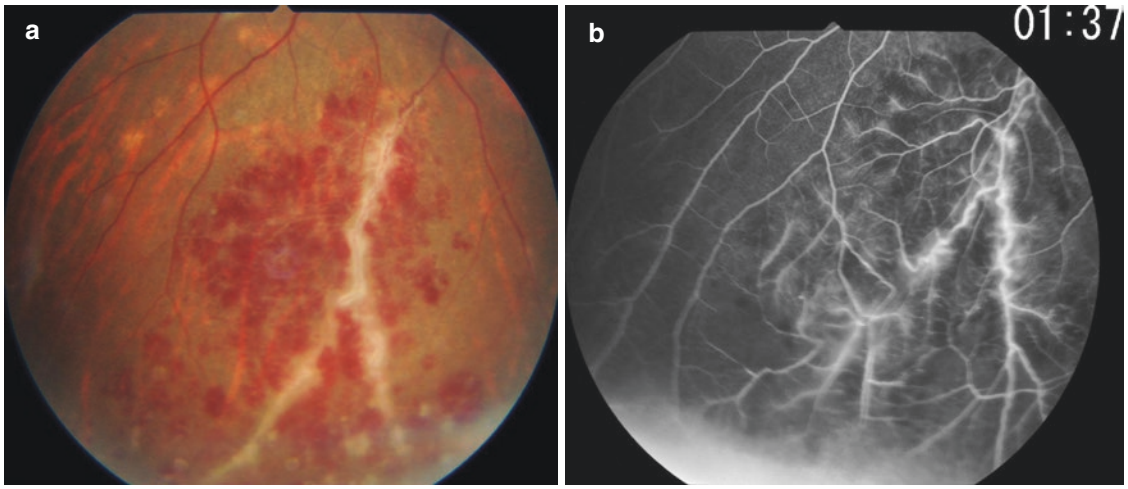

Fig. 11.12 (**a**) Severe sheath formation of the retinal vein surrounded by retinal hemorrhage. (**b**) Fluorescein angiography shows diffuse hyperfluorescence in the corresponding retinal vein

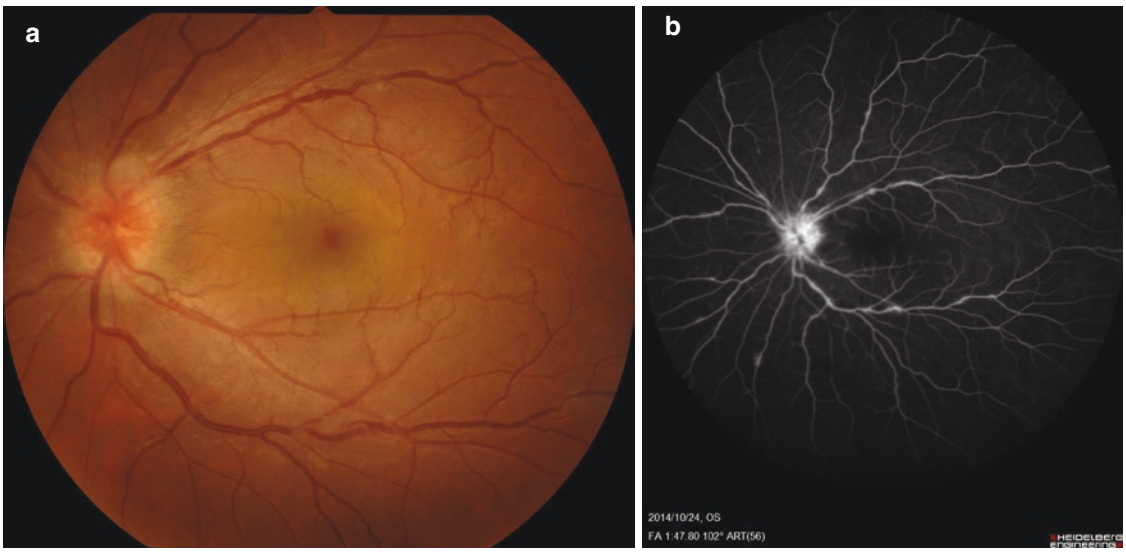

Fig. 11.13 (**a**) Optic disc swelling and only faint nodular periphlebitis are seen. (**b**) Fluorescein angiography shows nodular hyperfluorescence more than expected from the appearance of color fundus photo

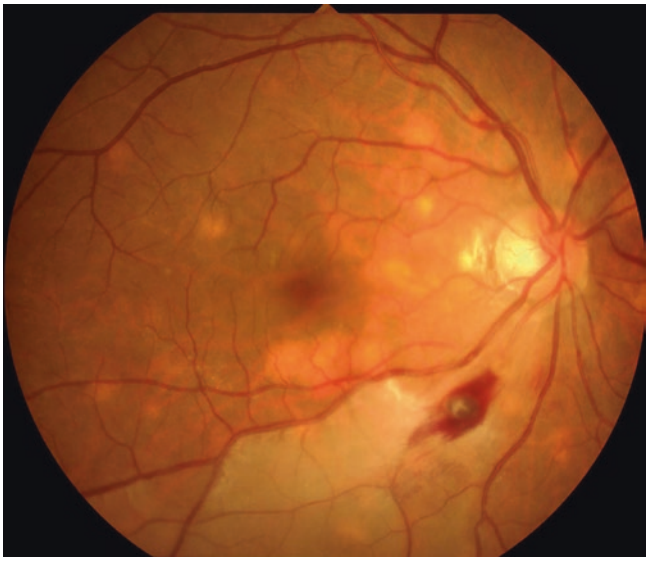

Fig. 11.14 A macroaneurysm is seen along with the temporal-inferior retinal artery. The peripheral retina is edematous suggesting the decreased retinal artery perfusion. Chorioretinal lesions in the deep layer of the retina are also present in the posterior pole

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