Kayser-Fleischer ring

Suvarna JC

ABSTRACT

Kayser-Fleischer (K-F) ring seen in Wilson's disease (WD) is due to copper deposition in the Descemet's membrane in the sclero-corneal junction. Although believed to be pathognomonic of WD, it may be seen in many other hepatic conditions and intraocular copper-containing foreign bodies. The K-F ring detected in pre-symptomatic cases of WD may lead to speedy diagnosis and early management. Co-relation of K-F ring to WD to the disease severity, disappearance with successful treatment, reappearance with non-compliant treatment may aid in optimum management of WD. The importance of K-F ring detection in first-degree relatives of the index case cannot be over-emphasized.

KEY WORDS: Corneal rings, Kayser-Fleischer ring, Wilson's disease

Kayser-Fleischer ring (K-F ring), also referred to as Fleischer-Kayser ring or Fleischer-Strumpell ring was first described by the German ophthalmologists Bernhard Kayser (1902) and Bruno Fleischer (1903) independently in a patient who was then diagnosed to have multiple sclerosis. Fleischer in 1912 recognized it as a part of Wilson's disease (WD). Early workers believed the corneal coloration to be due to endogenous deposition of heavy metals like silver and copper. This hypothesis was supported by the findings of large amounts of silver and copper in the viscera by Rumpel. Policard, Bonnet and Bonamour (1936) histospectroscopically demonstrated the presence of copper and the absence of silver in the region of the K-F ring. Work by Liebergall, Coleman, Sanders, Field (1963) supported this view. In 1970, Harry et al., described the electron microscopic appearance of the K-F ring as electron-dense deposits of copper of varying sizes lying mainly in the Descemet's membrane.

Description

The K-F ring is seen at the corneoscleral junction (limbus). Although it is commonly described to be golden brown or greenish yellow in color, it could be ruby red, bright green or ultramarine blue in color, sometimes interspersed with yellow or smoky brown color. It is usually bilateral and appears initially superiorly at the 10-2 o'clock position, then inferiorly and later becomes circumferential. It is best detected with slit-lamp examination by an expert, often with the aid of a goniolens. In later stages, it may be seen even with a flash-light.

The K-F ring starts as a sharp line where the endothelial pattern begins distinctly (Schwalbe's line - junction of the epithelium and endothelium), extending rarely more than 5 mm centrally and gradually fading towards the centre of the cornea. The variable position of the Schwalbe's line is probably the reason for the variability in the description of a clear ring of cornea peripheral to the K-F ring. The pattern of denser copper deposition at the periphery may be related to the direction of aqueous flow and/or functional peculiarity of the peripheral corneal endothelium. The K-F ring is believed to be formed by the copper particles which infiltrate into Descemet's membrane through the endothelial cells from the aqueous humor. The smaller particles coalesce over a period of time to give rise to larger deposits, granules which may or may not be in zones. This 'corneal chelate' accounts for the K-F ring. It is seen simultaneously in both eyes, when associated with systemic disorders. However, Innes et al. have reported a case of unilateral K-F ring in a patient with WD. This patient had a scarred eye (with low intraocular pressure and reduced aqueous production) which did not show the K-F ring. Hence they postulated that the copper deposition is through the aqueous (which was markedly reduced in the scarred eye), rather than limbal circulation (which was normal in the scarred eye). Moreover, it may not be just due to passive diffusion but may be attributed to cellular activity, the copper granule production being related to formation of the basement membrane by endothelial cells. Apart from the K-F ring in WD, the cornea is also permeated by ionic copper as demonstrated by spectroanalytic study and X-ray excitation spectrometry, which is independent of the appearance of the K-F ring and may aid in the diagnosis of WD.

Pathophysiology

WD is caused by mutation in the copper-transporting gene AT P78 which facilitates the transfer of copper into the Golgi apparatus where it combines with ceruloplasmin or other proteins like cytochrome oxidase. Failure of this process leads to instability and decreased half life of ceruloplasmin and...
paradoxical ceruloplasmin deficiency. The free circulating copper (which is toxic as it inhibits enzymatic processes) accumulates in liver cytosol resulting in hepatocyte degeneration and cirrhosis. When the sites for copper binding in the liver are saturated, free copper is released into the circulation and accumulates in other tissues like the eye, brain (basal ganglia) and kidneys amongst others leading to morphological changes, functional derangements and clinical manifestations: K-F ring in the cornea, sunflower cataract in the lens, tremors and rigidity due to accumulation in the central nervous system, and renal tubular defects due to accumulation in the kidneys.[10] The K-F ring is reported more frequent in H1069Q (most frequent mutation in WD in Hungary) homozygous patients, with higher mean age at diagnosis than patients heterozygous or negative for H1069Q.[6] This may suggest a genetic predisposition. Other hepatic conditions as listed above that prevent elimination of copper, or intraocular foreign bodies containing copper, lead to elevated free copper concentrations and K-F ring.

**Disappearance of K-F Ring**

As can be understood from its pathophysiology, the K-F ring results from deposition of copper in the cornea after hepatic stores have been saturated. Thus, the K-F ring may not be apparent in the early stages of WD. It is seen in only 40% of pre-symptomatic WD cases and 65-70% of WD cases with only hepatic manifestations.[7] In contrast, almost every patient of WD with neurological manifestations has the K-F ring. Wilson’s disease is treated with agents that chelate copper and hence the K-F ring could fade or disappear (80-90% cases) following successful treatment. The ring tends to disappear in the reverse order of its formation.[10] Patients with end-stage liver disease related to WD who undergo liver transplant also demonstrate a partial decrease in or complete disappearance of the K-F ring.[11] However, it should be noted that the disappearance or reduction is independent of the stage of the disease as also the effectiveness of copper chelation and is not a good predictor of clinical improvement in patients.[12] It may reappear with non-compliance, and occasionally even with successful maintenance therapy.[12]

**Differential Diagnosis and Variants**

WD (hepatolenticular degeneration/ Westphal-Strumpell disease/Westphal pseudosclerosis) is the most common cause of the K-F ring and was once thought to be pathognomonic of WD. However, K-F-like ring has been reported in many other conditions like cryptogenic cirrhosis,[13,14] chronic active hepatitis,[14,15] neonatal hepatitis,[14,15] primary biliary cirrhosis,[16] cholestatic cirrhosis,[17] hepatocellular disorders (when bilirubin rises acutely above 20mg/dl),[18] alcoholic liver disease,[19] galactosialidosis,[20] schistosoma infection,[21] multiple myeloma and intraocular foreign body containing copper.

The K-F ring can be confused with Fleischer’s ring, which is seen in keratoconus (conical cornea). It is a degenerative corneal condition seen more frequently in females (around puberty). It presents as an incomplete or complete, greenish or brownish ring seen in the peripheral cornea and increases in severity with age. The patient presents with decreased vision, photophobia, diplopia, visual distortion, asthenopia and glare around lights. The occurrence of Fleischer’s ring is related to iron deposition in basal epithelial cells. Slit-lamp biomicroscopy with cobalt blue filters and diffuse illumination demonstrates Fleischer’s ring well and corneal topography shows characteristic pear-shaped elongation of the central mires. These findings and clinical features will help to differentiate it from the K-F ring.[22]

**Importance of K-F Ring**

Identification of the K-F ring in any patient with unexplained central nervous system disease, poorly categorized psychiatric disorder, abnormal liver function tests, chronic active hepatitis, cirrhosis of liver, rickets, renal tubular acidosis, unexplained Coomb’s negative hemolytic anaemia, especially if there is a relative with WD or any of the conditions mentioned above should prompt the physician to undertake diagnostic workup for WD. At times, the K-F ring could be the first detectable manifestation of WD and in such rare instances, ophthalmologists play a critical role in the early recognition of WD. Larger K-F ring size may correlate with the severity of the disease, but not necessarily with the magnitude of urinary copper excretion.[23] It is one of the clinical parameters used in monitoring patients on therapy although its reduction is not necessarily a good predictor of clinical improvement. Its reappearance while on therapy may indicate non-compliance. Kayser-Fleischer ring detection is one of the screening tests for first-degree relatives of a WD index case. Early detection and treatment of WD may prevent the associated morbidity and mortality of the disease.

**References**

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