Kayser-Fleischer-like rings in patients with hepatic disease

Chetan Chhikara, Vijaya Pai H, Ganesh Pai C

Purpose: The aim of this work was to study Kayser-Fleischer [KF]-like rings in patients with hepatic or cholestatic liver disease and to find out the relation between serum bilirubin level and the presence of KF like ring in these patients. Methods: In this study, we evaluated patients with hepatic and cholestatic liver diseases with total Serum bilirubin levels >10 mg/dl. These patients were evaluated for the presence or absence of KF like ring. Results: A total of 67 patients with total bilirubin >10 mg/dl were included in the study. Patients were divided into 3 groups based on total S. bilirubin level: Group 1 with S. bilirubin >30 mg/dl, Group 2 with S. bilirubin >20 - <30 mg/dl and Group 3 with S. bilirubin >10 - <20 mg/dl at baseline evaluation. On follow-up they were divided into 3 groups based on the serum bilirubin level. Group 1- >20 mg/dl, Group 2- >10 - <20 mg/dl, Group 3- <10 mg/dl. KF like ring was seen in 98.5% of patients with high total S. bilirubin level. KF like ring disappeared in 87.5% of patients with reduction in the total S. bilirubin level to less than 10 mg/dl. Conclusion: KF like ring was seen in 98.5% of patients with high total S. bilirubin, disappeared in 87.5% of patients with reduction in the total S. bilirubin level to less than 10 mg/dl. There was no significant difference between the Total S. bilirubin levels, age, gender and KF Like Ring.

Key words: Bilirubin, hepatic disease, kayser fleischer like rings, kayser fleischer rings, wilsons disease

The Kayser-Fleischer (KF) ring is an ophthalmic finding seen secondary to systemic disease that causes dysfunction in copper metabolism. It is defined as a pigmented ring due to copper deposition in Descemet’s membrane. It is seen at the sclerocorneal junction mostly as golden brown/greenish yellow in color.[1] Though KF ring is pathognomonic of Wilsons disease, it is also seen in various other hepatic conditions. Detection of KF rings in asymptomatic cases can help in clinching early diagnosis and starting early treatment. KF ring is correlated with disease severity, disappears on treatment and reappears on discontinuation of the treatment. KF ring is initially evident at superior and then inferior corneal poles and becomes circumferential later. It begins as a sharp line where the endothelial pattern is seen distinctly (Schwalbe’s line). It rarely extends more than 5 mm centrally and starts fading towards the central cornea. The clear corneal ring seen around the KF ring depends upon the position of Schwalbe’s line.

Slit-lamp examination is considered the best for detection of the KF rings but it may be detected with torchlight in later stages. It resolves in 80% of the cases with chelation therapy over a period of 3–5 years.

KF like rings are rarely seen in other diseases but more recent data shows KF like rings are not that rare and seen in the following conditions: Cryptogenic cirrhosis, partial biliary atresia, active chronic hepatitis (autoimmune hepatitis), unexplained central nervous system disease, and Abnormal LFT’s (elevated bilirubin levels). In these conditions copper levels in the liver are less than 250 mcg/gram dry weight, normal 24 hr urinary copper, Ceruloplasmin levels are normal or slightly high. Table 1 shows the differences between KF ring and KF like ring.[2]

Fig. 1 shows Slit-lamp appearance of KF ring and KF like ring.[2]

Methods

This was a hospital-based observational study of the consecutive patients with hepatic and cholestatic liver diseases seen in Department of Gastroenterology, in a tertiary care hospital. All these patients were referred to the ophthalmology department for the presence of KF like ring. Institutional ethics committee clearance was obtained for the study. The study was conducted from August 2016 to August 2018. All the patients were explained regarding the study and the need to carry out the necessary tests. Consent was obtained from all the patients. The patients with hepatitis of any etiology, cholestasis of any etiology with serum bilirubin >10 mg/dl were included in the study.

Patients with non-hepatic renal disorders such as renal tubular acidosis, rickets, unexplained Coomb’s negative hemolytic anemia, poorly categorized psychiatric disorders,
Granular
Always circumferential
Not seen
May be seen
Absent
Descemet’s membrane
Peripheral stroma
Kayser-Fleischer-Like Rings (Bile pigment rings)

1: Differences between KF Ring and KF Like Ring

| Layer of cornea involved | Color          | Texture | Site of the ring | Naked eye Examination | Site of ring | Response to chelation therapy | Color | Texture | Site of ring | Naked eye Examination | Site of ring | Response to chelation therapy |
|-------------------------|----------------|---------|------------------|-----------------------|--------------|-------------------------------|-------|---------|--------------|-----------------------|--------------|-------------------------------|
| Descemet’s membrane     | Golden brown  | Granular| Superior/inferior/circumferential | May be seen         |              |                              | Yellowish green | Homogenous | Peripheral stroma | Not applicable       |              |                               |

Figure 1: Slitlamp picture showing the differences between KF ring and KF like ring

copper foreign body in the cornea or intraocular region, occupational exposure to copper or topical therapeutic use of copper-containing substance were excluded from the study.

All the patients underwent detailed evaluation for the assessment of KF like rings. A detailed history was taken from each patient including the duration of hepatic disease. Complete ophthalmic evaluation included slit-lamp examination to see the presence or absence corneal pigmented ring was done by an experienced ophthalmologist. If no ring was seen on slit-lamp examination, gonioscopy was done to confirm the presence of the ring. Systemic diagnosis and serum bilirubin levels were noted. Re-evaluation of the cornea was done at 2-4 weeks and 6-8 weeks after the first evaluation.

Results

A total of 67 patients participated in the study. 58 (86.6%) were males and 9 (13.4%) were females.

14 patients had malignancy [hepato cellular carcinoma, carcinoma pancreas, gall bladder carcinoma, cholangio carcinoma]. The other causes were alcoholic liver disease (15), viral hepatitis (7), liver failure (16), bile duct calculus (7), liver cirrhosis (3), cholangitis (3) autoimmune hepatitis (1) and Budd Chiart syndrome (1).

We classified the patients into 3 categories at the initial evaluation based on the total S. bilirubin level: Group 1- >30 mg/dl, Group 2- >20 - <30 mg/dl and Group 3- >10 – <10 mg/dl based on total S. bilirubin level. At baseline KF like ring was present in 10 patients in group 1, 14 patients in group 2 and 42 patients in group 3. One patient in Group 3 KF like ring was absent.

On follow-up, the patients were classified into the following 3 categories, based on total S. bilirubin level. Group 1- >20 mg/dl, Group 2- >10 - <20 mg/dl and Group 3- <10 mg/dl.

After receiving the appropriate treatment for the hepato-biliary disease by the gastroenterologist, patients were called for ophthalmology review, for the KF like ring at 2-4 and 6-8 weeks. A total of 49 (73.1%) and 22 (38.8%) patients came for first and second follow-up visits respectively. KF like ring was present in 34 patients (50.7%) and absent in 15 patients (22.4%) on 1st follow-up visit and present in 9 patients (13.4%) and absent in 13 patients (19.4%) during the 2nd follow-up visit. Four patients from Group 1, 5 patients from Group 2, 9 patients from Group 3 were lost to follow-up during the first follow-up. Seven patients from group 1, 9 patients from Group 2, 29 patients from Group 3 did not come for the second follow-up visit.

During the first follow-up, i.e., 2-4 weeks after the baseline evaluation there were 13 patients in Group 1, 12 patients in Group 2 who had KF like ring, while in Group 3, nine patients had KF like ring. It was absent in 15 patients.

During the second follow-up visit, 6-8 weeks after the baseline evaluation there were 4 patients in Group 1 and 3 patients in Group 2 who had KF like ring, while in Group 3 there were 2 patients who had KF like ring. It was absent in 13 patients and these 13 patients belonged to Group 3. Table 2 shows number of patients in the different groups.

During the first follow-up, 18 patients moved to higher bilirubin group, 27 remained unchanged, 4 patients moved to group with lesser total S. bilirubin group. During the second follow-up, 4 patients moved to higher bilirubin group, 14 remained unchanged, 4 moved to lesser total S. bilirubin group. 18 (26.86%) patients were lost to follow-up after the baseline examination. The mean survival time of the KF like ring was found to be 55.076 days and the median survival time of the KF like ring was found to be 45 days.

Kaplan-Meier Estimate (Survival Curve) showed disappearance of KF like ring in 13 (59.09%) patients out of 22 that came for follow-up by 6-8 weeks after initial diagnosis (second follow-up). The KF like ring persisted in the remaining patients (9; 40.90%) beyond this time period. Cox Regression Analysis revealed that the hazard ratio of KF
like rings for age, total bilirubin level and gender were not statistically significant (P value >0.05; Table 3).

Discussion

Wilson’s disease is caused by a defect in ATP7B protein product that occurs because of mutations in the chromosome 13q14 which leads to impaired copper metabolism that requires lifelong treatment once the diagnosis is established.

Kayser-Fleischer ring has been an important finding for the early diagnosis of Wilson’s disease and initiating treatment. There have been case reports suggesting the role of increased bilirubin levels for the presence of pigmented corneal rings called “Bile Rings” or “KF Like Rings”. Correlation of increased bilirubin levels with pigmented rings was supported by normal Serum Copper studies in these patients.[3]

Therefore, it is important to differentiate the nature of these KF like rings from KF rings that are seen due to copper deposition, before starting the treatment with chelation therapy and avoid potential adverse effects due to treatment. The aim of our study was to find out the determinants of KF like rings in patients with hepatic or cholestatic liver disease.

A. Nagral et al. in their study of forty adult patients with acute hepatitis of prolonged duration had K-F like rings. All the patients had increased levels of total bilirubin (>20 mg/dl) for over 6 weeks duration (ranging from 15–45 days).[3] All the patients underwent naked eye and slit-lamp examination of the eyes by a single experienced ophthalmologist. 37 patients had K-F like ring out of total 40 patients. A repeat slit lamp examination was done when serum bilirubin decreased to <10 mg/ld. The K-F like rings disappeared in all the patients. In their study, they did not specify the time period after which patient was examined and the levels of bilirubin at that time.

In our study we re-examined the patients at a specific time interval after the baseline examination. We included all the patients with bilirubin more than 10 mg/dl as compared to 20 mg/dl in study by A. Nagral, et al. In our study KF like rings were present in 66 patients out of 67 patients at baseline examination. 13 patients had KF like rings on sequential follow-ups with total bilirubin <10 mg/dl. In our study we included patients without considering the duration of the disease, whereas A. Nagral et al. included all the patients with prolonged acute hepatitis that can affect the nature of KF like rings.

Mahreema Jawairia et al. reported a case of a 29-year-old male of Hispanic origin with history of cryptogenic cirrhosis in past. Ceruloplasmin and serum copper concentrations were found to be normal and patient had no clinical features of Wilson’s disease. Laboratory investigations showed high excretion of copper in urine but it was quite less than the levels found in symptomatic cases of WD.[3]

The exact nature of these rings could not be determined, and they were considered as KF like rings. They did not mention the bilirubin levels in their case report.

In our study, we included all the patient’s with hepatic and cholestatic liver disease. Wilson’s disease was ruled out as all the patients had normal copper studies. Earl J Williamsa et al. presented a case report on KF like rings in alcoholic liver disease and concluded that alcoholic liver disease should be considered as the differential diagnosis of a patient presenting with liver disease and KF like rings.[4] In our study 19 patients with alcoholic liver disease had KF like rings which supported the findings of the above case report.

Lee M. Weinberg et al. presented a case with severe cholestasis with fluctuating KF like ring and concluded that all the patients with severe cholestasis and KF like ring should be evaluated for serum copper levels.[3] Similar findings were seen in 14 patients in our study.

Frommer D et al. presented 3 cases having KF like rings without Wilson’s disease. They concluded that KF Ring could no longer be considered as pathognomonic for the diagnosis of Wilson’s disease.[4] In our study we included 67 patients’ without Wilson’s disease with total Bilirubin levels >10 mg/dl at baseline and 66 out of 67 patients had KF like rings without WD.

Richard Fleming et al. evaluated four cases in their study, three patients’ with primary biliary cirrhosis and one patient with aggressive chronic hepatitis with cirrhosis. All the patients had pigmented corneal rings. Urinary copper excretion, serum and hepatic ceruloplasmin levels were significantly raised in cases of Primary biliary cirrhosis. Diagnosis of Wilson’s disease was ruled out by studies conducted with radio Copper (64Cu/65Cu) in patients diagnosed with Primary biliary cirrhosis that showed plasma disappearance curves with secondary rise in radio Copper due to binding with ceruloplasmin. They concluded that pigmented corneal rings can be seen in primary biliary cirrhosis and chronic active liver disease and need to be differentiated based on the clinical presentation and laboratory investigations.[5]

Table 2: Showing number of patients in each group at baseline evaluation, first follow-up, second follow-up visit

| Bilirubin level (mg/dl) | KF like ring present | Number of patients |
|------------------------|----------------------|--------------------|
| At Baseline            |                      |                    |
| >30                    | 10                   | 0                  |
| >20–<30                | 14                   | 0                  |
| >10–<20                | 42                   | 1                  |
| At First Follow-Up Visit|                      |                    |
| >20                    | 13                   | 0                  |
| >10–<20                | 12                   | 0                  |
| <10                    | 9                    | 15                 |
| At second Follow-Up Visit|                      |                    |
| >20                    | 1                    | 0                  |
| >10–<20                | 3                    | 0                  |
| <10                    | 2                    | 13                 |

Table 3: Statistical analysis by Cox regression analysis, Kaplan Mier analysis

| Variables        | SE   | P     | Hazard ratio | 95.0% CI for Exp (B) Lower | Upper |
|------------------|------|-------|--------------|---------------------------|-------|
| Age              | 0.027| 0.935 | 1.002        | 0.951                     | 1.057 |
| Bilirubin difference | 0.044| 0.536 | 1.028        | 0.942                     | 1.121 |
| Sex              | 0.774| 0.075 | 3.973        | 0.871                     | 18.110 |
Richard Fleming et al. did not correlate the pigmented corneal rings with bilirubin levels. In our study serum and urinary copper levels were within normal limits in all the patients and none of the patients had clinical features of Wilson’s disease.

Showkat Ali Zargar et al. reported a case of a 9-year-old boy with autoimmune chronic active hepatitis. Diagnosis of WD was suggested by the presence of active liver disease, KF like ring and elevated hepatic copper. WD was excluded by normal serum and urine copper and serum ceruloplasmin levels.

They concluded that presence of KF like ring in non-Wilsonian liver disease strongly suggests that this ring is no longer considered absolutely diagnostic for WD and abnormalities of copper metabolism must be documented to establish the diagnosis of Wilson’s disease. In our study we had one patient diagnosed with autoimmune hepatitis and was found to have KF like ring on examination. In our study we made an attempt to see the level of bilirubin over a time period and time taken for the disappearance of ring in these patients. This may help to give more specific value of total bilirubin levels required for the appearance of KF like ring.

Though the presence of KF like rings was more in patients with total bilirubin levels >10 mg/dl, but the incidence did not reach the statistical significance in our study. There have been few case reports KF like rings in past but none of the studies have followed up the patients at regular interval. Our study is the first to correlate the KF like rings with duration of decline in bilirubin levels and gender of the patient along with total bilirubin levels. Only one patient did not have KF like ring with total bilirubin level more than 10 mg/dl at baseline examination. This patient had very low direct bilirubin levels and that may be an important factor for the absence of KF like ring. Limitations of our study are small sample size and the loss of follow-up of 18 patients on first follow-up visit and 32 patients on second follow-up visit. Still more studies with more sample size are required to confirm the findings of this study. 14 patients were diagnosed to have malignancy at presentation, could be the reason for follow-up loss and in the others could be that recovery from the disease may be the reason to miss the follow-up visit.

Phinney RB et al. demonstrated yellowish staining of 3 pairs of donor cornea after they were dissected from the whole globe. All three patients from which eyes were enucleated had increased serum bilirubin levels for at least 1 month before death.[8]

Absorbance spectrum of bilirubin was seen in corneal and scleral eluates on spectrophotometric analysis. Slit-lamp examination of the cornea showed yellow pigmentation of corneal stroma. Peripheral cornea showed more pigmentation than the central cornea. They concluded that yellow pigmentation of cornea can be seen in patients with jaundice.

Sridhar MS, et al. used anterior segment optical coherence tomography (AS OCT) to assess the KF ring.[10] However, we did not do AS OCT in our patients.

Conclusion
Kayser Fleischer like ring was seen in 98.5% of patients with high bilirubin. KF like ring disappeared in 87.5% of patients with reduction in the bilirubin level less than 10 mg/dl. No differences were found in the patient’s age and KF like rings.

To conclude more similar studies with large sample size are required to support the findings of this study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Suvarna JC. Kayser-Fleischer ring. J Postgrad Med 2008;54:238-40.
2. Nagral A, Jhaveri A, Nalawade S, Momaya N, Chakkarwar V, Malde P. Kayser-Fleischer rings or bile pigment rings? Indian J Gastroenterol 2015;34:410-2.
3. Jawairia M, Subhani M, Siddiqui G, Prasad A, Shahzad G, Rizvon K, et al. Unexplained findings of kayser-fleischer-like rings in a patient with cryptogenic cirrhosis. Case Rep Gastrointest Med 2012;2012:438525.
4. Williams EJ, Gleeson D, Burton JL, Stephenson TJ. Kayser-Fleischer like rings in alcoholic liver disease: A case report. Eur J Gastroenterol Hepatol 2003;15:91-3.
5. Weinberg LM, Brasitus TA, Lefkowitch JH. Fluctuating Kayser-Fleischer-like rings in a jaundiced patient. Arch Intern Med 1981;141:246-47.
6. Frommer D, Morris J, Sherlock S, Abrams J, Newman S. Kayser-Fleischer-like rings in patients without Wilson’s disease, Gastroenterology 1977;72:1331-5.
7. Fleming CR, Dickson ER, Wahner HW, Hollenhorst RW, McCall JT. Pigmented corneal rings in Non-Wilsonian liver disease. Ann Intern Med 1977;86:285-8.
8. Zargar SA, Thapa BR, Sahni A, Mehta S. Kayser-Fleischer like ring in autoimmune chronic active hepatitis. Indian J Gastroenterol 1991;10:101-2.
9. Phinney RB, Monondo BJ, Abraham A. Corneal icterus resulting from stromal bilirubin deposition. Ophthalmology 1989;96:1212-4.
10. Sridhar MS, Rangaraju A, Anbarasu K, Reddy SP, Daga S, Jayalakshmi S, et al. Evaluation of Kayser–Fleischer ring in Wilson disease by anterior segment optical coherence tomography. Indian J Ophthalmol 2017;65:354-7.