Review 1#

Comment: The authors studied the relationship between gastric xanthelasma and metabolic disorders in Chinese patients. Several minor questions are raised. First, in the text discussing table 1, you should mention that your 99 patients are the only patients whom gastric biopsy was performed, and the 99 non-xanthelasma patients are control. Although you had mentioned in later section 3.3 in your text, it seems not chronologically which may confuse the readers. Second, in page 10, what is the difference between non-gastric gastrointestinal xnthelasma and extra-gastrointestinal xanthelasma? Third, in page 13 the 2nd line from the bottom, the hematoma means liver hemangioma? Finally, what is the number of each group in table 4?

Reply: Thank you for precious comment. First, sorry for the confusion and description of Table 1 was modified; Second, non-gastric gastrointestinal xanthelasma refers to xanthelasma within GI tract, but not located in stamch, while extra-gastrointestinal xanthelasma refers to xanthelasma other than GI tract, such as skin xanthelasma or eye xanthelasma and this information was added in the text; Third, sorry for the mistake, and it was hemangioma, rather than hematoma; Finally, each group included 99 subjects.

Review 2#

Comment: This work by Drs. Chen et al., have studied gastric xanthelasma and metabolic disorders in a large retrospective study among Chinese population. They collected patient information from endoscopy archives and analysis the relationship of xanthelasma with several biochemical, metabolic and tumor markers. The work is the first of its kind in Chinese population and appears interesting and novel. Similar studies in Korea and Japan have been reported, and the role of xanthelasma and its possible implication in disease pathogenesis is still under investigation. It is not clear regarding its formation mechanism and importance in gastric disease pathogenesis at this stage, authors noted its link with gastric atrophy, dysplasia and a few

biochemistry factors. Two important questions remain as follows, 1. H. pylori infection rate appears pretty low in the samples collected in table 2, which is around 30%, this is even lower than the infection rate in general population, which is around 50%, how to explain this phenomenon? 2. Without a clear known mechanism of its formation, it is hard to explain the correlation of xanthelasma with identified biochemical and tumor markers, authors are encouraged to discuss more about this area, and provide information on how to clarify its role in disease pathogenesis and, therefore makes the paper in-depth and more attractive. Minor points: A number of typos and grammar errors are present throughout the text that requires authors' attention to revise.

Reply: Thank you for precious comment. First, Hp infection rate in China ranged from 25% to 90% among population. Cities in the east and south China witnessed a relative low Hp rate. So, our study was conducted in Hangzhou, Zhejiang, relative lower Hp detection rate might be explained by better hygiene and lower contamination. Second, current understanding of mechanism in xanthelasma formation is that xanthelasma is manifestation of local lipid metabolism disorder affected by systemic metabolic factors (such as ROS, ox-LDL, et al) and inflammatory factors. So our analysis focused on both circulatory metabolic and inflammatory factors in this concern and provided a preliminary support. Further analysis will be conducted to investigate local lipid profile, immune cell infiltration, cytokines secretion to dig deep into mechanism of xanthelasma. Finally, the manuscript was carefully retrieved by all authors and grammar errors were corrected.

Review3#

Comment: The article is of interest due to large number of cases .But several points need clarification: It is sometimes not clear that where endoscopic or pathologic confirmation of xanthelasma were the basis of grouping patients and analysis. The higher age of patients with xanthelasma should have been documented with statistical test whih is nit the case considering the information in table 2. Presentation symptoms

of abdominal discomfort , dyspepsia , abdominal distension etc . all are in the same category. It could be of interest to know whether the presentation symptom was different between those with xanthelasma and those without. The pathologic classification of IM should be referenced. To my knowledge the classification includes complete and partial and the groups mentioned in the text are not familiar to me. Instead dysplasia should be classified to high , intermediate and low grade. The control group was mentioned to be 99 healthy controls who were collected from annual health examination but in table 3 many of the control goup had various medical diseases . I suggest that the control group be selected among those who had endoscopies if their metabolic data are available.

Reply: Thank you for precious comment. First, sorry for the confusion, and description of endoscopic or pathologic defined patients were now clearly presented now. Second, Table 2 included information about age in two groups. And we found that xanthelasma tended to be slightly elder than control group but with no significant difference. Third, patients with xanthelasma usually presented with GI tract-related symptoms and that would sure be interesting in identifying symptoms besides GI tract. But unfortunately, we did not see any patients with complains other than those listed. Fourth, definition of metaplasia was added in Method section. And our ‘high grade’ was supposed to refer to complete and ‘low’ together with ‘medium’ means partial. We did not do categorize dysplasia group as for limited subjects. Finally, 99 controls selected in this analysis were people who took annual health examination (including blood routine, biochemical, tumor marker, abdominal ultrasound, endoscopy, et al) in our hospital. Comorbidity with other metabolic diseases were found in both groups. Before clear understanding of xanthelasma pathogenesis, exclusion of patients with these diseases might be confounding.