Discussion Summaries

Should we be concerned about histologic changes caused by novel submucosal injection agents used for EMR and ESD?

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Discussion Summaries

Abstract

Normal saline mixed with dyes is a widely used submucosal lifting agent for endoscopic resection of small gastrointestinal (GI) lesions. For larger GI lesions, novel agents are used to achieve optimal results. ORISE gel is a novel, premixed submucosal lifting solution for endoscopic resection procedures. The initial histologic appearance of endoscopic specimens with injection of ORISE gel is characterized by a pale, basophilic amorphous appearance which has the potential to be misinterpreted as a pathologic finding. The histologic appearance changes overtime to an eosinophilic appearance that is reflected by an inflammatory, foreign body reaction.

We summarize the @GIJournal discussion held on May 12, 2021, about the article by Olivas et al “Histologic changes caused injection of a novel submucosal lifting agent for endoscopic resection in GI lesions” ¹. The guest experts to discuss pathology included Drs. Emma Furth (EF), and Pallavi Patil (PP), the discussion was moderated by Dr. Dmitriy Kedrin (DK).

Discussion Summaries

Introduction

Novel submucosal agents have been developed to improve the duration of the submucosal cushion for endoscopic resection of larger gastrointestinal lesions. These solutions are viscous and have a greater dissipation time. ORISE gel is a premixed submucosal agent containing a polysaccharide and saline solution mixed with a dye. It received FDA (Food and Drug Administration) approval in 2018 for endoscopic resection of gastrointestinal lesions. Case series have been reported to describe the histologic findings in resected specimens injected with ORISE gel. These case series have demonstrated the potential for misinterpretation as pathologic findings including amyloid deposition and mucinous adenocarcinoma.^{2 3 4}

The recent article “Histologic changes caused injection of a novel submucosal lifting agent for endoscopic resection in GI lesions”¹ is a retrospective review of the histological appearance of specimens from 43 patients who underwent resection of gastrointestinal lesions with ORISE gel injection. There was a total of 63 specimens: 51 Endoscopic mucosal resection (EMR), 7 Endoscopic submucosal dissection (ESD) and 5 surgical. In the endoscopically resected specimens that were evaluated initially, ORISE gel appeared as an amorphous, pale basophilic material present in submucosa in all cases. The pattern was readily distinguishable from normal saline solution. Histologic characteristics in surgical specimens demonstrated extensive deposits of undulating, amorphous, eosinophilic material with associated multinucleated giant cells.¹

The histologic pattern of ORISE gel is acellular and granular, is negative to stains (PAS and mucicarmine), is readily distinguished from saline as compared to the mucinous pattern which is stranded and strongly positive to stains.

This case series reports a difference from recent reports where the pattern of ORISE gel is described as bubbly, with submucosal hemorrhage and weak positivity to mucicarmine. In this case series no hemorrhage was seen with the ORISE gel pattern.^{3 4} The histologic pattern of ORISE gel changes dramatically over time consistent with a robust inflammatory response by a degrading gel product. The lack of vascular involvement rules out amyloid deposition.

Limitations of the study included lack of quantification of ORISE gel injected into specimens. Most specimens reviewed were EMR specimens. Majority of the specimens were obtained from the colon and rectum.

Discussion Summaries

The authors conclude that the characteristic histologic findings and the clinical context can be used to avoid misinterpretation as a pathologic finding.

Discussion

On a poll conducted by @Gijournal before the discussion, 415 votes were cast for the preferred lifting agent of choice. Results were as follows:

Q1. Were there cases when using a lifting solution makes diagnosis less certain? With reference to depth of invasion, progression towards dysplasia, etc.? Does it lead to a novel diagnosis due to presence of a giant cell reaction?

@GIPathJC Often there is no trouble, sometimes in serrated polyps it was difficult to determine a sessile serrated polyp vs hyperplastic polyp, or a submucosal lipoma. For the most part, the diagnosis was certain.

Q1a. @ijlakbar Would you say proprietary lifting agents help instead in path diagnosis?

PP In some cases it is easy to determine margins and complete resection when lifting agent is used.

Discussion Summaries

@PAPatilMD PP Sessile serrated lesion lifted with ORISE with associated submucosal lipoma (left), better representation of the lipoma in another focus (right) 5/13/21 1625
<https://tinyurl.com/3ebxjspk>

EF While it has not hampered diagnoses, cannot state if the agent helps.

Q1b. @SultanMahmoodMD I guess another question is that if the lifting agent is not specified or mentioned, would it make the job difficult for the pathologist? We use templates all the time and usually they do not include lifting agent type.

EF We spend a lot of time and effort sorting out artifacts. By letting us know these agents were used is important

@GIPathJC Agree more information is always helpful and contributes to making a more accurate assessment.

Q1c. @SultanMahmoodMD The authors mentioned mucinous adenocarcinoma has some similarity? Should we avoid ORISE gel when we suspect cancer?

@TeamCaptainJohn Highly unlikely to confuse lifting agent with mucinous adenocarcinoma microscopically. Biggest differential is spread of acellular pools from low-grade appendiceal mucinous neoplasms more so than invasive mucinous carcinoma.

Discussion Summaries

@GiPathJC In very big polyps, it may be prudent to consider an immediate backup option of resection.

@GiPathJC Would opine EMR could be considered when possible. Mucin is simple to distinguish from lifting agents.

Q2. Can you think of other examples where new endoscopic technology might have caused changes in how you view specimens submitted?

@GiPathJC Sometimes margins assessment is difficult, especially if specimen is not pinned. If it is a larger EMR, pinning helps with inking and grossing to better assess margins. Otherwise, it gets rolled up and is hard to ink or determine margins.

Q2a @TarunRustaGI_MD How about the intramucosal carcinoma in the esophagus?

PP In the esophagus there can be duplication of muscularis mucosa in Barrett's esophagus making assessment of submucosal invasion challenging on biopsies only when intramucosal adenocarcinoma is the term used.

Q3. So it seems no special stains are necessary to identify submucosal lift agent, as long as pathologist is aware of the lift?

@GiPathJC For the most part, no special stains would be needed. ORISE is easy to distinguish from Amyloid.

EF Correct. Knowing the agent was used negates our chasing to identify this material with stains. We are aware of its appearance and actually know it was used even if not stated. We would confirm by reading the clinical record including endoscopic reports.

Discussion Summaries

@PAPatilMD PP ORISE with giant cell reaction in a submucosal lymphoid aggregate (left), ORISE with giant cell reaction in sub serosal fat (right) 5/13/21 1616 <https://tinyurl.com/5b6ry4tn>

Conclusion

Novel submucosal injection solutions have a characteristic histologic appearance. The histologic appearance is unlikely to be misinterpreted as a pathologic finding for mucinous adenocarcinoma or amyloid. Clearly identifying the lifting agent used in endoscopic procedure templates can be a valuable source of information for the pathologist to avoid any confusion. Usually, no special staining is required to distinguish novel submucosal injection solutions on the pathology.

Discussion Summaries

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