Editorial Commentary

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Acute appendicitis: A continuing challenge for both clinicians and pathologists

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Acute appendicitis represents one of the most common abdominal inflammatory diseases in paediatric surgery. Nevertheless, although it is the most common diagnosis leading to surgical intervention in emergency abdominal surgery, a discrepancy between preoperative diagnosis and histopathological findings is evident.[1,2] Especially in the paediatric population, pre-surgical diagnosis is challenging due to potential atypical clinical presentation in this age group, non-specific clinical symptoms and also a wide range of differential diagnoses. Therefore, considerable efforts have been made to identify suitable clinical and laboratory tests to corroborate the diagnosis of appendicitis.[3] In this context, a combination of white blood cell count (WBCC) and C-Reactive Protein (CRP) should become routine practice, which could be fully supported even in view of differential diagnoses and a potential inflammatory state of the organism. However, concerning the accurate diagnosis of appendicitis some concerns from the pathological viewpoint could give further perspectives to this diagnostic challenge. Thus, the histopathologically negative appendix is well documented and controversially discussed.[1,4] From the viewpoint of a pathologist it is important to recognize that for the pathological diagnosis the entire specimen of the appendix will not be analysed histologically. Routinely, the tip of the appendix, a cross-section from the resection zone and one cross-section from the zone which macroscopically gave evidence of inflammation are taken for histological analysis. The macroscopical signs of inflammation of the appendix are given by the accompanying inflammatory reaction of the serosa with hyperaemia of the subserosal vessels, fibrin exudation or even perforation. Thus, in routinely analysed appendectomy specimens it is possible to overlook an early appendicitis in cases in which the mucosa erosion –one important prerequisite for the diagnosis of acute appendicitis- is not visible in the histological slides. An early pathological analysis of negative appendectomy specimens by Stambolis and Wagner (1985) clearly demonstrated that in this case a further re-evaluation of the entire appendix could minimize the cases of negative appendectomies.[5] In this context it is interesting to note that even the interpretation of pathologists might be incorrect, especially in negative appendices.[2]

Another important issue in the accurate diagnosis of acute appendicitis is the fact that appendicitis is an inflammatory disease with different stages which follow the basic pathophysiology of inflammation, with margination and transmigration of inflammatory cells from the microcirculation in the inflamed tissue. It is important to realize that the traffic of inflammatory cells is regulated by cell adhesion molecules. Thus, following leukocyte margination from the centre of the blood stream to the periphery, rolling on the endothelium is mediated by the cell adhesion molecule, E-selectin, and the transmigration of the inflammatory cells mediated by Intercellular Cell Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1).[6] Taking these experimental findings together, we were able to demonstrate some time ago that the different stages of appendicitis correlate with the expression of cell adhesion molecules, and that especially the expression of E-selectin is an important prerequisite for the accumulation of inflammatory cells in the inflamed appendix.[7] Thus, it was concluded that for the diagnosis of an inflamed vermiform appendix the expression of E-selectin is mandatory, and that a histologically negative appendix does not totally exclude the diagnosis of appendicitis.[2] The same situation applies to the interpretation of laboratory parameters, since Gronroos (2001) concluded from his results that a negative CRP does not exclude acute appendicitis in children.[8] In the search for exact and safe preoperative diagnostic tools, knowledge of the molecular basis of inflammation

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in the appendix could give an innovative input for further studies. From the pathological viewpoint future prospective studies should take into account three further elements: (i) extended histological analyses in primarily negative appendices, (ii) histopathological analysis by two independent pathologists and (iii) comparison of the clinical data and the histological report with immunohistochemical findings. For such prospective studies the results of retrospective findings are important to help develop a potential panel of laboratory parameters which should then be tested in prospective studies. However, one of the most challenging issues for such prospective analyses will be the question of how safe a predictive preoperative laboratory and clinical testing could be and, perhaps the most important challenge, in which cases surgery should be postponed. Especially in the paediatric population this question is from major importance.

From the viewpoint of a paediatric surgeon, the accuracy of preoperative diagnosis of acute appendicitis remains a predicament since the surgeon is supposed to avoid both negative appendectomy and delays in treatment. Historically, the diagnosis of acute appendicitis was, and still is, primarily a clinical diagnosis based on patient history and physical examination. Laboratory tests, and in particular CRP and WBCC, are routinely performed as two widely measured inflammatory markers. However, patients who had acute appendicitis with either normal leukocyte counts or no elevation in CRP level have become common knowledge in surgical practice.[3,8] Clinical scores for appendicitis, e.g. the Alvarado score, the Ohmann score, the Paediatric Appendicitis Score, or standard pathways in diagnostic protocol are useful tools in the evaluation of suspected acute appendicitis.[3,9,10] In the last two decades, preoperative radiological imaging, specifically abdominal sonography and computed tomography (CT), improved the diagnostic accuracy for acute appendicitis.[11-14] CT imaging for acute appendicitis, despite its high accuracy, is not our preferred diagnostic tool in a paediatric population because of the need to minimize radiation. Abdominal ultrasound in children has increased both sensitivity and specificity of the diagnosis of acute appendicitis, particularly in centres with considerable experience, along with its cost-effectiveness, easy access and avoidance of radiation. Unfortunately, this imaging modality is not yet routinely available on a 24-h basis either in developing countries or in some so-called developed countries. At our institution, abdominal ultrasound has become a routine and very useful diagnostic tool in equivocal cases of appendicitis in children.

In conclusion, appendicitis remains a challenge not only for surgeons but also for pathologists. With a view to clinical science, preoperative diagnosis and pathological analysis of appendicitis always represent a useful combination which could significantly improve patient care for a general clinical problem, especially in the paediatric population.

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