What is positive appendicitis? A new answer to an old question. Clinical, macroscopical and microscopical findings in 200 consecutive appendectomies

Hussain A, Mahmood H, Singhal T, Balakrishnan S, El-Hasani S

ABSTRACT

Introduction: The correlation between clinical and histopathology findings in appendicitis has been highlighted by many studies. However, the impact of this correlation on the surgical decision to remove a normal-looking appendix is still vague, with no clear definition of positive appendicitis. The aim of this study was to correlate the histological, operative and clinical diagnoses of acute appendicitis (AA).

Methods: 200 patients with a preoperative diagnosis of AA underwent laparoscopic appendectomy. A single consultant surgeon performed all the procedures. The clinical, macroscopical and microscopical outcomes were reported and analysed. Follow-up assessment was performed as an outpatient appointment.

Results: 112 women and 88 men were included in this study. The mean age was 18.8 (range 8–83) years. Macroscopical appendicitis was confirmed in 139 (69.5 percent) patients, while microscopical appendicitis was reported in 147 (73.5 percent) specimens of the appendix. Ten (7.2 percent) out of 139 patients who were macroscopically positive were found to have a normal appendix on microscopical examination. Different pathologies were found in 21 (10.5 percent) patients, and all underwent appendectomy. Microscopical appendicitis was confirmed in 10 (25 percent) out of 40 patients who had a normal-looking appendix.

Conclusion: The correlation of the clinical, microscopical and macroscopical findings in AA is important in order to understand the natural history of appendicitis, and this may help to formulate a sound surgical decision. These findings are supportive of justifying appendectomy for normal-looking appendices, if no other pathology is found.

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INTRODUCTION

Appendectomy is the treatment of choice for acute appendicitis (AA) which has a morbidity of 3.1%. With perforation, the morbidity is varied but can reach up to 47.2%, while the mortality rate is less than 1%.[1] The high morbidity rate is due to a delay in presentation and initiation of active treatment, as well as patient factors. AA is a potential risk for patients due to the life-threatening complications. Therefore, careful assessment at emergency departments is mandatory to avoid preventable complications associated with AA.[2] Observation has improved the ability to distinguish patients with appendicitis from those without, while negative explorations are related to improper assessments based mainly on the findings of the clinical examination rather than on other related signs and symptoms, as well as the inflammatory markers status.[3,4] The correlation between the clinical and histopathology findings in AA has been considered as the main criteria to nominate positive appendicitis. The aim of this study was to evaluate the clinical, macroscopical and microscopical findings and the postoperative course for patients with a clinical diagnosis of AA, and to determine whether these findings should influence the surgical decision for clinical right iliac fossa pain.

METHODS

This study included 200 consecutive patients (112 female and 88 male) who were admitted under the care of single consultant surgeon between September 1999 and January 2007. The clinical diagnosis and the timing of the appendectomy had been made by the surgeon who was not blinded to the preoperative imaging studies required in some patients. The inclusion criteria included all patients who were admitted with a diagnosis of AA (including complicated appendicitis) and who

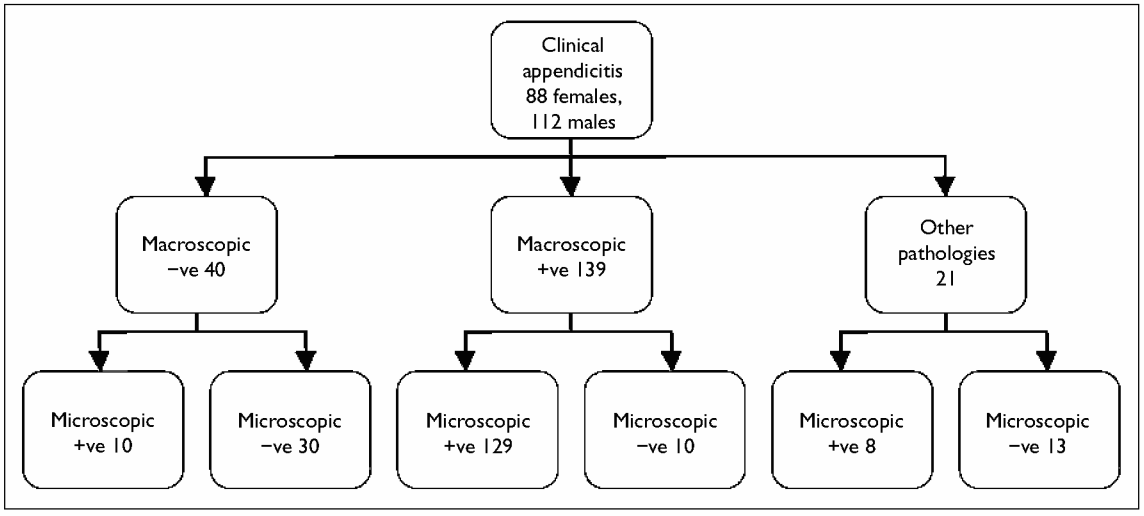

Fig. 1 The flow chart of the results.

underwent laparoscopic appendectomy, regardless of age, gender, American Society of Anaesthiologists status and the degree of inflammation of the appendicitis. All operations were performed by a single surgeon to avoid bias, and the outcome reflected a defined level of surgical experience. Open appendectomies, which are usually done by other surgeons in our department, were excluded to avoid selection bias. All operations were done using the laparoscopic approach; hence, there was no bias regarding the intraoperative diagnosis and other pathologies.

AA, which refers to the inflammation of the appendix, was evaluated by the surgeon macroscopically and confirmed on histopathological examination of the specimen. An appendix was considered normal-looking when there was no macroscopical sign of inflammation. A true-positive was a macroscopically- and microscopically-inflamed appendix, while a true-negative was a macroscopically- and microscopically-normal appendix. A false-positive was a microscopically-normal but macroscopically-inflamed appendix, while a false-negative was a microscopically-inflamed appendix which was evaluated as normal on macroscopical examination by the surgeon (Fig. 1).

The diagnosis of AA and the decision to operate depended mainly on the clinical picture and investigations, such as white cell count, C-reactive protein level, abdominal and pelvic ultrasonography, and sometimes computed tomography (CT), especially in females of childbearing age and in borderline cases. Antibiotics were used only in complicated appendicitis, such as perforated appendicitis. Standard histological examination was conducted for all specimens. No immunohistochemical staining was performed, and three consultant pathologists reported the specimen findings. Clinical, macroscopical (operative) and microscopical (histopathology) data were collected and analysed. If a normal appendix was found during laparoscopy, all abdominal organs, including the small bowel and adnexias in women, were examined. Patients who had a normal appendix on histological examination were not subjected to further investigations unless they developed persistent symptoms. All patients were followed up postoperatively by a single outpatient visit, usually two weeks after discharge. They were advised to call or to ask their general practitioners to refer them in cases of persistent symptoms or development of complications. The very low rates of mid- and long-term complications were assessed according to the time of occurrence, and they were not an issue in this study.

RESULTS

200 patients were admitted with the diagnosis of AA and underwent appendectomy. A total of 112 women and 88 men were included in this study. The mean age was 18.8 (range 8–83) years. Macroscopical appendicitis was confirmed in 139 (69.5%) patients, while microscopical appendicitis was reported in 147 (73.5%) specimens. Ten (7.2%) out of the 139 patients who were macroscopically positive were found to have a normal appendix on microscopical examination. Different pathologies were found in 21 (10.5%) patients, but all underwent appendectomy as well. If these were to be excluded, the false-positive rate would be 45.0% (18/40). Clinically, the positive rate was 82.1% (147/179), while macroscopically, the true-positive rate was 92.8% (129/139), the false-negative rate was 29.5% (18/61), while the false-positive rate was 7.2% (10/139). Normal microscopical examination was

reported in 53 (26.5%) patients. In 179 (89.5%) patients, the right iliac fossa pain and other symptoms resolved after appendectomy. Further investigations were arranged for one patient due to persistent symptoms. Macroscopical appendicitis was confirmed in all nine (4.5%) patients who had a preoperative CT diagnosis of AA. Histological examination confirmed appendicitis in all these patients. No conversion to open appendectomy was made.

Table I. The true- and false-positive and negative rates.

Category	No. (%) of patients
True-positive	129/139 (92.8)
False-negative	10/40 (25.0)
False-positive	10/139 (7.2)
True-negative	30/40 (75.0)
Total	179/200 (89.5)

DISCUSSION

With advances in technology and imaging modalities, the diagnosis of AA has improved, with a subsequent significant reduction in negative appendectomy, especially for females of childbearing age. Surgical experience is another factor that influences the accuracy of diagnosis and proper treatment of appendicitis; thus a single consultant had made the diagnosis and treatment in our series. It is not uncommon to find a normal-looking appendix during operation, and this requires surgeons to diagnose a cause for the right lower quadrant (RLQ) pain. However, in many patients, no intra-abdominal abnormality is found in spite of a full exploration and evaluation of the pelvic organs. Surprisingly, the histopathological examination of the removed appendices reveals normal findings. Very few patients are subjected to imaging or contrast study to evaluate persistent postoperative pain or delayed recovery.

Many studies recorded a positive microscopical AA of 64.6%–91%.[5-8] Some authors have suggested that using a minimally-access approach (macroscopical diagnosis) was reliable, as a false-negative error rate of 3% had been reported when comparing macroscopical and microscopical findings at laparoscopy, while the discrepancy between the surgeon's opinion of the macroscopic appearance of the appendix and the pathologist's opinion (which was assumed to be the most accurate) was reported in 14.5% of the cases in another study.[9,10] Laparoscopy significantly reduces the rate of removal of histologically-normal appendices.[11] For macroscopically-inflamed appendices, the false-negative rate was lower, while the false-negative rate of macroscopically-normal appendices was 45.0% after the exclusion of 21 patients who had been diagnosed with other pathologies (Fig. 1). This high rate had raised the question of the accuracy of macroscopical diagnosis, which conflicted with the findings of Kraemer et al, which supported the accuracy of macroscopical diagnostics during laparoscopy.[9]

The experience of the surgeon is important in predicting positive appendicitis, and it is easier in an acute setting with clear macroscopical signs of inflammation. However, it is difficult to assess an appendix which looks normal on exploration. A significant number of these patients presented acutely because of recurrent symptoms, making it impossible to differentiate between acute and non-acute appendicitis (chronic or grumbling appendicitis) based only on the operative findings. One of the main issues in the management of AA is whether or not to proceed with appendectomy, if a normal-looking appendix is found during exploration. Laparoscopy has been suggested as an investigation tool to reduce the cost of negative exploration for AA.[12] The use of modern imaging, such as ultrasonography and CT to improve the accuracy of diagnosis and to reduce negative appendectomy rates, has been confirmed in many studies.[13-16] However, there are conflicting reports, suggesting that negative exploration and the rate of perforation are not decreasing in spite of modern imaging modalities and laparoscopy.[17,18] This is related to the time of presentation, clinical approach and team experience.

In a study of 1,026 patients who underwent appendectomy, there were 110 (10.5%) false-positive decisions (range 4.7%–19.5%). Of the 916 patients with appendicitis, 170 (18.6%) false-negative decisions were made (range 10.6%–27.8%).[19] Some authors concluded that the removal of a normal-looking appendix at emergency laparoscopy for RLQ pain was unjustified, and that the decision should be based on other factors, including age, comorbidities and clinical presentation.[20-22] The principle here is that appendectomy should not add an extra risk to critically-ill, paediatric or elderly patients. Although there are significant clinical and financial costs incurred by patients undergoing negative appendectomy, there is also a significant number of these patients showing a complete clinical response to appendectomy with acceptable morbidity,[23] as in our study. The other benefits of this approach are the prevention of further episodes of RLQ pain, resulting in reduced admission and management cost, as well as the prevention of complications of misdiagnosed AA.

The dilemma continues even after the introduction of laparoscopic appendectomy. van den Broek et al reported that 9% of their series continued to have recurrent

RLQ pain after negative laparoscopy, yet they did not recommend appendectomy in these patients.[21] However, due to the consistently false-negative rate of diagnostic laparoscopy and the low morbidity rate for laparoscopic appendectomy, Chiarugi et al supported incidental appendectomy in patients with RLQ pain,[24] as we have done. A true-positive rate of 64.58% was seen in 1,718 out of 2,660 appendectomy specimens in another study. More than 93% of these patients were asymptomatic at their long-term follow-up, and about 75% presenting with pain in the RLQ showed histological evidence for chronic appendicitis.[25] These criteria include chronic inflammatory changes in the wall of the appendix, resulting in structural changes in the abdominal cavity. The clinical correlate exists only in relation to the serious changes resulting from the inflammation of the appendix, such as fixations and adhesions. Therefore, chronic appendicitis must be assumed in cases of recurrent or persistent pain lasting longer than seven days, and an elective appendectomy should be recommended.[26]

In view of these findings, and while there was no difficulty in diagnosing AA in the majority of male patients, surgeons facing acute RLQ abdominal pain in female and male equivocal cases have two options: either to wait and see while subjecting these patients to ultrasonography or CT, or to proceed with diagnostic laparoscopy. Based on our experience, we performed diagnostic laparoscopy and imminent appendectomy routinely for clinical AA in both male and female patients with classical presentation, provided no other cause was found during exploration. For women who had borderline clinical findings, normal ultrasonography, CT and gynaecological examination were also included in addition to diagnostic laparoscopy and appendectomy.

We suggest removing a normal-looking appendix when there is no abnormality on operative exploration. This is because 9% (18/200) of specimens of macroscopically-normal appendices were found to be microscopically inflamed, according to our findings (Fig. 1). If we excluded the 139 patients with obvious macroscopically-inflamed appendices and the 21 female patients who were diagnosed with pathologies other than AA, the percentage of the microscopically-inflamed appendices would be 45%, which represented a high false-negative rate. On the other hand, 20 out of 139 (14.4%) specimens of macroscopically-inflamed appendices were found to be normal on histological examination. Therefore, a decision not to remove normal-looking appendices would mean either to leave 45% of the patients with an inflamed appendix and possible dangerous complications, or to remove these appendices by accepting that 10% are histologically-normal appendices, which is the safe approach advised by the authors. The readmission rates as well as post-appendectomy complications, such as adhesion colic and pelvic abscesses, should also be considered.

Surgeons who decide not to remove normal-looking appendices for patients presenting with suspected AA, may treat these patients postoperatively with antibiotics. Although the outcome of this approach is generally acceptable, the problem of a long hospital stay, improper use of resources, the possibility of recurrence of the same symptoms and considerable anxiety for the patient, family and surgeon, are the main disadvantages. Interestingly, Wang et al demonstrated that tumour necrosis factor alpha (TNF-α) and interleukin-2 (IL-2) expression are sensitive markers of inflammation in appendicitis. A significant number of histologically-normal appendix specimens (22.5%) showed increased cytokine expression, indicating an inflammatory reaction. Therefore, normal-looking appendices have a 22% chance of being inflamed on further sophisticated investigations.[27] This further supports the theory of removing normal-looking appendices when no confirmed intra-abdominal pathology for the RLQ pain is found during exploration with laparoscopy or laparotomy.

According to our findings, 20% (40/200) of patients who were admitted acutely because of clinical suspicion of AA and who underwent appendectomy, responded very well to appendectomy in spite of a normal microscopical examination of the appendix. Because no antibiotics was used in this group of patients and the placebo effect of surgery was equally affected in our series, the findings in this specific group of patients had raised the question of underlying cause. For example, appendix colic, appendicular feacolith and functional appendicular abnormality or functional appendicopathy might be the contributory factors rather than acute inflammation. 21 patients who had a normal appendix at operation were diagnosed with other pathologies. These included ruptured graffian follicle, ovarian cyst, pelvic inflammatory disease, post-laparotomy adhesions, endometriosis, mesenteric lymphadenitis and carcinoid tumour of the appendix. The appendectomy had resolved the right iliac fosa pain in the majority of the patients. Delay in recovery and persistent pain were only reported for patients who had been diagnosed with pathologies other than appendicitis.

There were two major groups of patients with AA in our series: (1) true-positive patients who were diagnosed macroscopically and microscopically with an abnormal appendix, and there was no question about proceeding with appendectomy in this group (Table I); (2) a group

of 33 true-negative patients (16.5%), admitted with a diagnosis of AA and had normal macroscopical and microscopical examinations, in which the appendectomy resolved their acute symptoms (only one patient needed further investigations after appendectomy).

Consequently, a concept of positive appendicitis would mean not only macroscopically and histologically positive findings, but also the opposite (i.e. normal macroscopical and histological findings). Further comprehensive blinded randomised controlled studies are needed to answer the question of whether a normal appendix should be removed during exploration for right iliac fossa pain, provided no other pathologies were identified. A comparison of operative and nonoperative control groups to show how many of such patients would improve with and without an operation, is also needed. This study has not considered the laparoscopic assessment of appendicitis, although a laparoscopic approach was used for the series. The message of the study is to remove the appendix of patients who present with right iliac fossa pain, if no other definite pathologies are found to account for the patients' symptoms.

In conclusion, the correlation of the clinical, macroscopical and microscopical findings in AA is important to formulate a sound surgical decision. Appendectomy has cured acute symptoms in most patients with normal microscopical appendicular examinations, and imaging and operative findings. Removing a normal-looking appendix during exploration for right iliac fossa pain should be considered when no other abdominal pathology is confirmed. We suggest that the term, "positive appendicitis" be used when appendectomy cures the symptoms and signs of clinical AA, irrespective of histological findings. Further comprehensive randomised studies are required to confirm our findings.

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