Clinical Case

Phlegmonous Appendicitis With Normal Bilirubin and Procalcitonin: Evidence of Compartmentalized Inflammation

Apendicite Fleimonosa com Bilirrubina e Procalcitonina Normais: Evidência de Inflamação Compartimentalizada

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ABSTRACT

Acute appendicitis is commonly evaluated using systemic inflammatory biomarkers, including C-reactive protein, procalcitonin, and serum bilirubin, to estimate disease severity and guide clinical decision-making. However, the relationship between local pathological severity and systemic biomarker response is not always consistent. We report a case of a 48-year-old premenopausal woman presenting with clinical features of acute appendicitis and elevated inflammatory markers, including C-reactive protein, but with normal serum bilirubin and procalcitonin levels. The patient underwent appendectomy, and intraoperative findings were consistent with acute inflammation without perforation. Histopathological examination confirmed acute phlegmonous appendicitis with transmural neutrophilic infiltration and localized fibrinopurulent peritonitis. Microbiological cultures yielded *Bacteroides fragilis* and *Enterococcus* species, supporting a polymicrobial localized infection. Incidental appendiceal endometriosis was identified in

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the subserosal region and confirmed by immunohistochemistry (CK7, ER, PR, CD10). Despite advanced local inflammation, the absence of hyperbilirubinemia and normal procalcitonin levels suggests limited systemic inflammatory involvement in this case. This observation supports the concept of compartmentalized inflammation in acute appendicitis, where severe local disease may occur without systemic biomarker elevation. Clinically, this highlights that normal bilirubin and procalcitonin values do not exclude advanced appendiceal inflammation and should be interpreted cautiously. The coexistence of appendiceal endometriosis appears incidental, reflecting the complexity of local pathological substrates rather than a definitive etiological factor. This case underscores the importance of integrating clinical, laboratory, and histopathological findings in the assessment of appendicitis severity.

Keywords: Appendectomy; Appendicitis; Bilirubin; Biomarkers; Procalcitonin

RESUMO

A apendicite aguda é comumente avaliada utilizando biomarcadores inflamatórios sistêmicos, incluindo proteína C-reativa, procalcitonina e bilirrubina sérica, para estimar a gravidade da doença e orientar a tomada de decisões clínicas. No entanto, a relação entre a gravidade patológica local e a resposta dos biomarcadores sistêmicos nem sempre é consistente. Relatamos o caso de uma mulher pré-menopáusica de 48 anos que apresentou características clínicas de apendicite aguda e marcadores inflamatórios elevados, incluindo proteína C-reativa, mas com níveis normais de bilirrubina e procalcitonina séricas. A paciente foi submetida a apendicectomia, e os achados intraoperatórios foram compatíveis com inflamação aguda sem perfuração. O exame histopatológico confirmou apendicite fleimonosa aguda com infiltração neutrofílica transmural e peritonite fibrinopurulenta localizada. As culturas microbiológicas revelaram *Bacteroides fragilis* e espécies *de Enterococcus*, corroborando uma infecção polimicrobiana localizada. Endometriose apendicular incidental foi identificada na região subserosa e confirmada por imuno-histoquímica (CK7, ER, PR, CD10). Apesar da inflamação local avançada, a ausência de hiperbilirrubinemia e os níveis normais de procalcitonina sugerem um envolvimento inflamatório sistêmico limitado neste caso. Essa observação corrobora o conceito de inflamação compartimentalizada na apendicite aguda, em que uma doença local grave pode ocorrer sem elevação de biomarcadores sistêmicos. Clinicamente, isso destaca que valores normais de bilirrubina e procalcitonina não excluem inflamação apendicular avançada e devem ser interpretados com cautela. A coexistência de endometriose apendicular parece ser incidental, refletindo a complexidade dos substratos patológicos locais em vez de um fator etiológico definitivo. Este caso ressalta a importância da integração de achados clínicos, laboratoriais e histopatológicos na avaliação da gravidade da apendicite.

Palavras-chave: Apendicectomia; Apendicite; Bilirrubina; Biomarcadores; Procalcitonina

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

- Acute appendicitis severity is commonly assessed using systemic inflammatory biomarkers, including C-reactive protein, procalcitonin, and serum bilirubin.
- Hyperbilirubinemia and elevated procalcitonin levels have been associated with complicated appendicitis and systemic inflammatory response.
- Appendiceal endometriosis is a rare condition, typically identified incidentally during histopathological examination and may clinically mimic acute appendicitis.

WHAT DOES THIS STUDY ADD?

- Demonstrates that advanced localized appendiceal inflammation can occur despite normal serum bilirubin and procalcitonin levels, supporting the concept of compartmentalized inflammatory response.
- Highlights the limitation of systemic biomarkers in excluding severe local disease, with direct implications for surgical decision-making.
- Shows that appendiceal endometriosis in this context is likely incidental, emphasizing the need to distinguish coexisting pathological findings from causal mechanisms.

INTRODUCTION

Acute appendicitis remains one of the most common surgical emergencies, yet accurate assessment of disease severity continues to rely on a combination of clinical evaluation, imaging, and laboratory biomarkers. Among these, systemic inflammatory markers, including C-reactive protein, procalcitonin, and serum bilirubin, are frequently

used to estimate the extent of inflammation and to differentiate between uncomplicated and complicated forms of appendicitis.[1] In particular, hyperbilirubinemia has been proposed as a surrogate marker of systemic inflammatory response and endotoxemia,[2] reflecting hepatic dysfunction secondary to bacterial translocation.[3] However, the relationship between local pathological severity and systemic biomarker response is not uniform, and discrepancies between these domains are increasingly recognized.

Emerging evidence suggests that acute appendicitis may not represent a single continuum of disease progression but rather a heterogeneous spectrum of inflammatory phenotypes.[4] In this context, severe localized inflammation may develop in the absence of a significant systemic response, indicating a compartmentalized inflammatory process confined to the appendix and surrounding tissues.[4] Such dissociation challenges the assumption that normal systemic biomarkers reliably exclude advanced local disease and has direct implications for clinical decision-making.

Appendiceal endometriosis is an uncommon entity, most often identified incidentally during histopathological examination of appendectomy specimens.[5,6] Although it may mimic or coexist with acute appendicitis, its role in the pathogenesis of appendiceal inflammation remains uncertain.[7] Rather than acting as a primary etiological factor, it may represent a local structural or microenvironmental substrate within a broader and heterogeneous inflammatory landscape.

We report a case of acute phlegmonous appendicitis with localized fibrinopurulent peritonitis in which serum bilirubin and procalcitonin levels remained within normal limits. The coexistence of incidental appendiceal endometriosis in this setting provides an opportunity to explore the concept of compartmentalized inflammation and to emphasize the potential limitations of systemic biomarkers in reflecting local disease severity.

CASE REPORTS

A 48-year-old premenopausal woman presented with a 48-hour history of progressively worsening abdominal pain. The pain initially originated in the epigastric region and subsequently migrated to the right lower quadrant. Laboratory investigations demonstrated a white blood cell count of 9.1 × 10^9/L with a neutrophil-to-lymphocyte ratio of 5.14. C-reactive protein was elevated (78.8 mg/L), with a CRP/albumin ratio of 1.97. Serum sodium level was 137 mmol/L, and procalcitonin was within the normal range (0.05 ng/mL). Serum bilirubin values were within normal limits, including total bilirubin (14.7 µmol/L), direct bilirubin (2.5 µmol/L), and indirect bilirubin (12.2 µmol/L). Peripheral blood smear analysis was unremarkable. Preoperative gynecological examination revealed regular menstrual cycles. The most recent Papanicolaou smear, performed four months prior to admission, was normal. Transvaginal ultrasound demonstrated a uterus in anteverted flexed position with an anteroposterior diameter of 40 mm and an endometrial thickness of 11 mm. The right ovary was normal in appearance and contained two unruptured follicles measuring 23 mm and 28 mm, respectively. The patient had a history of two spontaneous vaginal deliveries. The patient underwent an open appendectomy. Intraoperatively, findings were consistent with acute inflammation without evidence of perforation. Microbiological cultures obtained from a swab of the appendiceal lumen and a segment of mucosa yielded growth of *Bacteroides fragilis* and *Enterococcus* species.

Histopathological examination confirmed acute phlegmonous appendicitis with localized fibrinopurulent peritonitis in the stage of organization, accompanied by incidental appendiceal endometriosis, as described below.

Histopathological findings: Gross examination revealed an appendix measuring 3.5 × 1.2 cm with attached mesoappendiceal adipose tissue up to 1.8 cm in width. The serosal surface appeared opaque and was partially covered by purulent deposits. Representative tissue samples were processed in two paraffin blocks for histopathological evaluation. Microscopic examination demonstrated an appendiceal wall with ulcerated mucosa and hemorrhagic-purulent luminal content. A dense acute inflammatory infiltrate composed predominantly of polymorphonuclear leukocytes was present and extended transmurally through all layers of the appendiceal wall, spreading into the periappendiceal adipose tissue, consistent with acute phlegmonous appendicitis. The serosal surface was covered by fibrinopurulent exudate in the stage of organization, indicating a localized peritoneal inflammatory reaction. No areas of transmural necrosis or perforation were identified (Fig. 1).

In sections obtained from the distal portion of the appendix, cystic glandular structures lined by a single layer of columnar epithelium were identified in the subserosal region, surrounded by a delicate endometrial-type stroma. These structures were morphologically consistent with endometriosis of the vermiform appendix (Fig. 2). Immunohistochemical analysis demonstrated strong positivity for cytokeratin 7 (CK7) in the glandular epithelium, estrogen receptor (ER) and progesterone receptor (PR) expression in both glandular

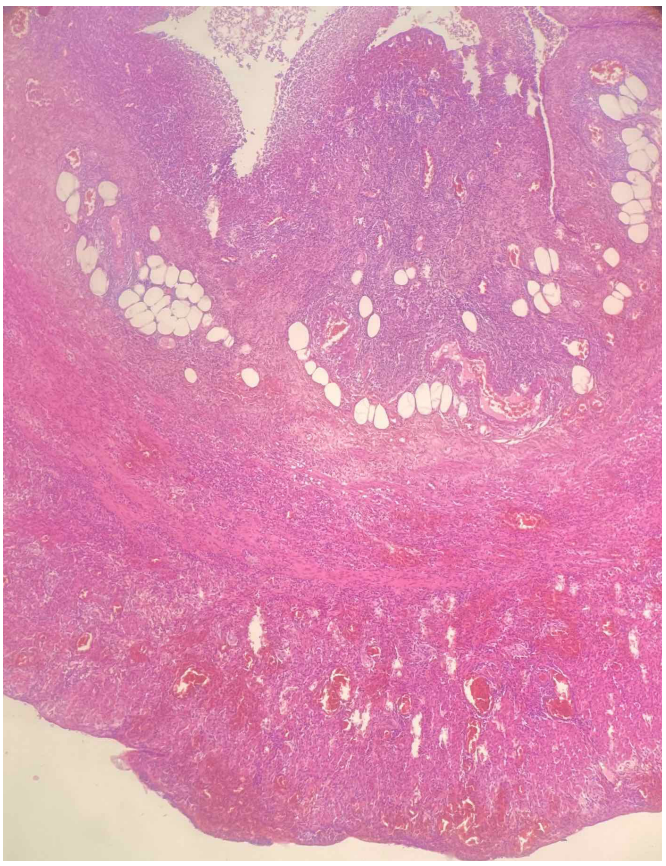

Figure. 1: H&E ×40. Acute phlegmonous appendicitis with transmural neutrophilic infiltration extending into the periappendiceal adipose tissue and fibrinopurulent exudate on the serosal surface.

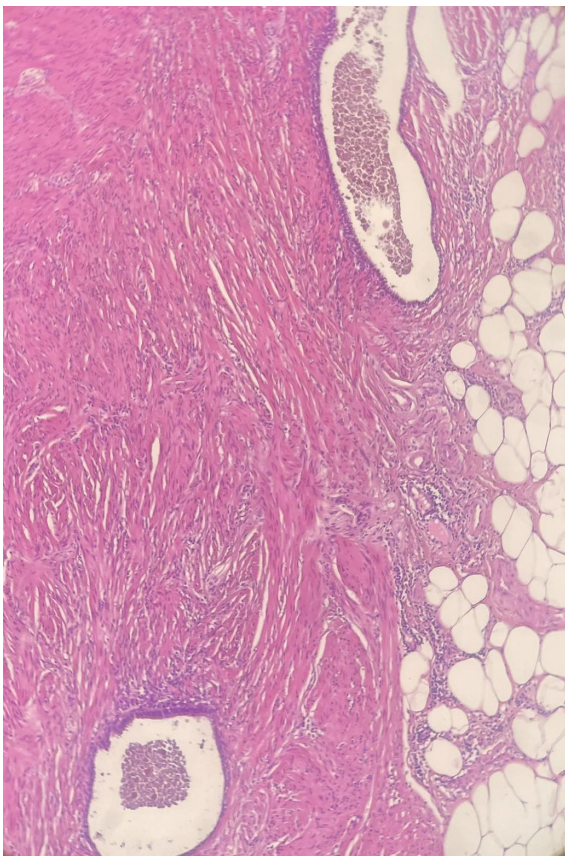

Figure. 2: H&E ×100. Subserosal endometrial glands with surrounding endometrial stroma, consistent with appendiceal endometriosis.

and stromal components, and CD10 positivity in the stromal cells, confirming the diagnosis of appendiceal endometriosis (Fig. 3).

DISCUSSION

Appendiceal endometriosis is an uncommon finding, most frequently identified incidentally during histopathological examination of appendectomy specimens.[5,6] Although it has been described as a potential cause of right lower quadrant pain or appendiceal obstruction, its clinical significance remains variable and, in many cases, uncertain.[5-7] The coexistence of appendiceal endometriosis with acute appendicitis has been reported in the literature; however, most cases remain descriptive and do not provide clear insight into the underlying inflammatory mechanisms or their clinical implications.[6-8]

The present case is informative not because of the presence of appendiceal endometriosis itself, but because of the observed dissociation between the severity of local inflammation and the absence of systemic biomarker response.[1,2] Histopathological examination confirmed acute phlegmonous appendicitis with transmural neutrophilic infiltration and localized fibrinopurulent peritonitis, indicating a significant local inflammatory process. Despite this, serum bilirubin and procalcitonin levels remained within normal limits, suggesting the absence of systemic inflammatory dissemination or endotoxemia.

This discrepancy supports the concept that acute appendicitis may manifest as distinct inflammatory phenotypes rather than a uniform, linear progression from mild to severe disease. In this framework, systemic biomarkers such as bilirubin and procalcitonin reflect the degree of systemic involvement, particularly bacterial translocation and endotoxin-mediated hepatic dysfunction, rather than local tissue inflammation alone.[3,9,10] Hyperbilirubinemia in appendicitis has been associated with endotoxin-induced impairment of hepatocellular transport systems,[3,11] while elevated procalcitonin levels are linked to systemic bacterial infection.[2,12] These mechanisms imply that biomarker elevation depends on systemic dissemination rather than the mere presence of localized inflammation. The absence of these alterations in

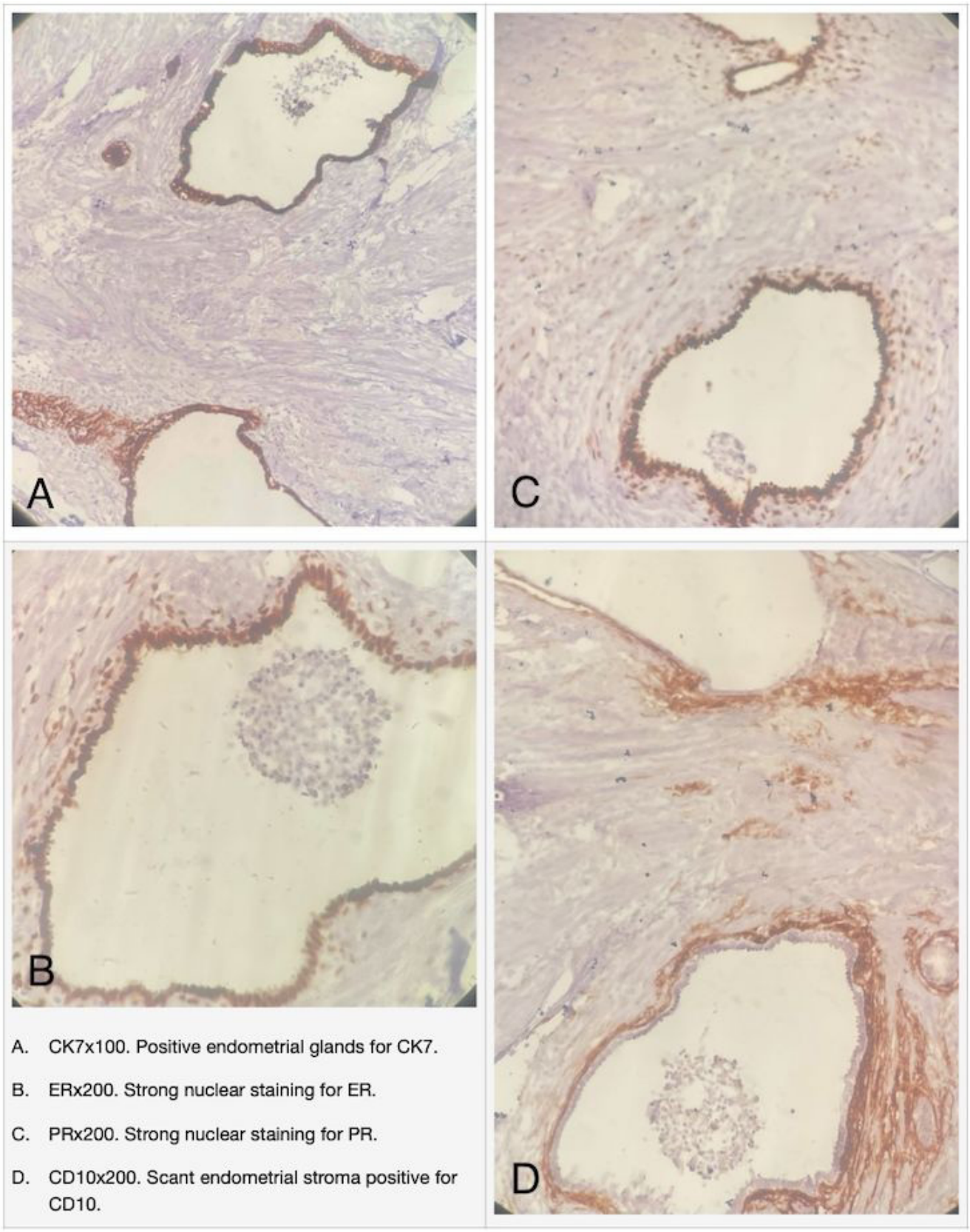

Figure. 3: Immunohistochemical confirmation of appendiceal endometriosis. (A) Cytokeratin 7 (CK7), ×100: strong cytoplasmic positivity in the epithelial lining of endometrial glands. (B) Estrogen receptor (ER), ×200: diffuse strong nuclear staining in endometrial glandular cells. (C) Progesterone receptor (PR), ×200: strong nuclear positivity in the glandular epithelium. (D) CD10, ×200: focal positivity in the surrounding endometrial-type stromal cells. The combined immunophenotype (CK7+, ER+, PR+, CD10+) supports the diagnosis of appendiceal endometriosis.

the present case, despite advanced local pathology, suggests that the inflammatory process remained compartmentalized within the appendiceal and periappendiceal region. This observation further supports the concept that systemic biomarker elevation reflects a threshold phenomenon related to inflammatory dissemination rather than a linear function of local tissue injury.

From a clinical perspective, this observation has important implications. Surgeons frequently rely on laboratory markers to support risk stratification and decision-making in patients with suspected appendicitis. However, this case demonstrates that normal bilirubin and procalcitonin values do not exclude severe localized disease, including phlegmonous inflammation and localized peritonitis.[1,13,14] Therefore, laboratory findings should be interpreted cautiously and always in conjunction with clinical assessment and imaging, particularly in patients with evolving or persistent symptoms.

The role of appendiceal endometriosis in this case warrants careful interpretation. Although it is tempting to consider ectopic endometrial tissue as a contributing factor to appendiceal inflammation through mechanisms such as fibrosis, luminal narrowing, or hormonally mediated local irritation, definitive evidence for a causal relationship is lacking. In the present case, the endometriotic focus was located in the subserosal region and did not demonstrate features of extensive infiltration or direct luminal obstruction. Consequently, it is plausible that the endometriosis represents an incidental finding rather than a primary driver of the acute inflammatory process. Nevertheless, its presence highlights the complexity of local pathological substrates that may coexist within appendiceal disease and potentially modulate local tissue response.

The microbiological findings, including isolation of *Bacteroides fragilis* and *Enterococcus* species, are consistent with the polymicrobial profile typically observed in acute appendicitis and further support the presence of a localized infectious process. Importantly, the absence of systemic biomarker elevation in this context reinforces the notion that microbial invasion and local inflammation do not necessarily translate into systemic inflammatory activation.

From a diagnostic standpoint, preoperative identification of appendiceal endometriosis remains challenging. Imaging modalities and routine clinical evaluation lack specificity for this condition, and in most cases, the diagnosis is established only after histopathological examination.[11] This underscores the continued importance of thorough pathological assessment of appendectomy specimens, not only for diagnostic completeness but also for identifying coexisting conditions that may have broader clinical relevance.

This report has inherent limitations, including its single-case design, which precludes generalization of findings. However, it serves as a hypothesis-generating observation supporting the concept of compartmentalized inflammation in acute appendicitis. Further studies integrating clinical, biochemical, microbiological, and histopathological data are needed to better define the relationship between local disease severity and systemic inflammatory response.

CONCLUSION

This case demonstrates that advanced localized appendiceal inflammation may occur in the absence of systemic biomarker elevation, supporting the concept of a compartmentalized inflammatory response in acute appendicitis. Normal serum bilirubin and procalcitonin levels do not exclude severe local disease, including phlegmonous appendicitis with localized peritonitis, and should therefore be interpreted with caution in clinical decision-making. The presence of appendiceal endometriosis in this setting appears to be incidental, highlighting the complexity of coexisting pathological substrates rather than a definitive causal relationship. Careful clinicopathological correlation remains essential for accurate interpretation of disease severity and underlying mechanisms.

LEARNING POINTS / TAKE-HOME MESSAGES

- Severe localized appendiceal inflammation may occur in the absence of systemic biomarker elevation, reflecting a compartmentalized inflammatory response.
- Normal serum bilirubin and procalcitonin levels do not exclude advanced appendicitis, including phlegmonous inflammation with localized peritonitis.
- Systemic biomarkers primarily reflect inflammatory dissemination and endotoxemia rather than the extent of local tissue involvement.
- Clinical decision-making in suspected appendicitis should integrate laboratory findings with clinical assessment and imaging, particularly in patients with evolving symptoms.
- Appendiceal endometriosis is often an incidental finding and should not be assumed to have a causal role in acute appendiceal inflammation without supporting evidence.
- Thorough histopathological evaluation remains essential for identifying coexisting pathological conditions and refining clinicopathological correlation.

ETHICAL DISCLOSURES

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RG: Bibliographic search, study design, data collection and drafting the article.
BK and IK: Data collection, analysis and interpretation of results.
GJ and VA: Study design and drafting the article.
All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

RG: Pesquisa bibliográfica, conceção do estudo, recolha de dados e redação do artigo.
BK e IK: Recolha de dados, análise e interpretação dos resultados.
GJ e VA: Conceção do estudo e redação do artigo.
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