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Isolated Perianal Fistulas: When and How Should I Investigate for Inflammatory Bowel Disease?

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Key Takeaways:

- Approximately, 5–10% of all perianal fistulizing Crohn's disease (PFCD) patients will have isolated PFCD. High or complex tracts, multiple internal openings, chronicity, and refractoriness to treatment—along with patient factors—should raise suspicion for PFCD (isolated or not).
- A negative initial luminal evaluation does not exclude CD — surveillance is key. Up to 25% of patients presenting initially with isolated complex fistulas develop luminal CD over time (median 2.5 years). Periodic reassessment with imaging, endoscopy, and symptom monitoring is critical to avoid missed or delayed diagnosis.
- Diagnosis and management of isolated PFCD requires a multidisciplinary, patient-centered approach. TOpClass criteria offer practical diagnostic guidance using clinical, radiologic, and histologic features. For patients with significant symptoms and complex isolated PFCD, anti-TNF therapy may be considered, though evidence is limited and optimal duration remains unclear.

Isolated Perianal Fistulas in Context

Perianal fistulas are a challenging manifestation of Crohn's disease (CD), affecting approximately one in five patients.[1,2] Perianal fistulizing Crohn's disease (PFCD) is associated with a complex disease course, distinct symptom burden, frequent need for surgical intervention, reduced quality of life, and increased healthcare utilization and costs.[3-5] Timely recognition and diagnosis are critical. Management strategies, both medical (e.g., anti-tumour necrosis factor (TNF) agents as first-line therapy) and surgical, differ significantly from those used for luminal CD alone and may prevent disease progression.[5-8]

Most PFCD cases present concurrently with or after a diagnosis of luminal CD.[9,10] However, in approximately 10% of patients, perianal fistulas appear in the absence of luminal inflammation.[11] Of these patients, we estimate that one-quarter will eventually manifest luminal CD, while 5–10% will remain as isolated PFCD.[10,11] Given that over 90% of perianal fistulas without luminal disease are cryptoglandular in origin, distinguishing PFCD in this context is diagnostically challenging.[12]

Cryptoglandular fistulas typically exhibit a simple anatomy—superficial, low-lying tracts with minimal sphincter involvement—and are more likely to heal.[2,12] In contrast, CD-related fistulas are often more complex, originating higher in the anal canal or rectum, with branching or multiple tracts, and are commonly refractory to standard treatment[2,12] Nonetheless, overlap exists: cryptoglandular perianal fistulas can be complex, and CD perianal fistulas can be simple. Importantly, no objective test currently exists to definitively distinguish CD-related from cryptoglandular fistulas.[13] This raises and important question: when—and how—should we evaluate for underlying inflammatory bowel disease (IBD)?

Evaluate the Nature of the Fistula

The first step in assessing a patient with an isolated perianal fistula is to carefully evaluate the nature of the perianal disease itself (**Table 1**). Features that should raise concern for PFCD include fistulas that originate high in the anal canal or rectum, have multiple internal openings, exhibit branching morphology, or present as multiple discrete fistulas. In addition to anatomy, fistula behaviour can also signal risk: fistulas that are chronic, recurrent, or refractory to treatment may be more likely associated with CD. The presence of other forms of perianal disease—such as strictures, ulcers, or fissures—further supports this suspicion, provided there are no alternative explanations such as infection, prior obstetric injury, or iatrogenic causes (e.g., from cancer-related procedures). Taken together, the anatomic complexity, clinical course, and associated perianal findings should all be considered in evaluating for potential PFCD.[13,14]

Assess Patient-level Risk Factors for CD

Beyond local findings, patient-level factors are essential in determining the likelihood of underlying IBD (**Table 2**). Younger age at fistula diagnosis, particularly under age 40, has been associated with an increased risk of CD in some studies.[11,13] A thorough clinical history should explore both current and past gastrointestinal symptoms, prior perianal disease, and any autoimmune or immune-mediated conditions, including extraintestinal manifestations of IBD and comorbidities such as hidradenitis suppurativa.[11,13,14] A detailed surgical history, including intestinal and perianal operations, as well as a family history of IBD, can provide further diagnostic clues.

During the physical examination, clinicians should assess for signs commonly associated with IBD, including ophthalmic and oral findings, and perform a comprehensive perianal exam to identify non-fistulizing manifestations such as skin tags, ulcers, or fissures. In selected patients, fecal calprotectin may serve as a useful adjunct.[13] While a normal result does not exclude CD in patients with high clinical suspicion, an elevated calprotectin level may prompt further evaluation in those with a lower pre-test probability of CD.

Comprehensive Luminal Evaluation

Once the decision is made to evaluate for CD (**Table 1**), the diagnostic workup should aim to definitively confirm or exclude the presence of luminal disease. This distinction matters: if CD is diagnosed, anti-TNF therapy is recommended as the first-line biologic treatment.

Ileocolonoscopy with segmental biopsies is the cornerstone for evaluating luminal disease—even in areas that appear endoscopically normal, as histologic inflammation may precede visible disease. We have observed cases of isolated perianal fistulas wherein we found histologic

Fistula characteristics	Other patient characteristics
Origin high in anal canal or rectum	Age <40 at fistula onset
Multiple internal openings	Family history of IBD
Branching or multiple tracts	IBD-related extraintestinal manifestations
Chronic, recurrent, or refractory course	Coexisting autoimmune or immune-mediated inflammatory diseases
Presence of non-fistulizing perianal disease (e.g. strictures, fissures, ulcers)	Prior intestinal or perianal surgeries
	Recurrent oral or genital lesions

Table 1. Fistula and patient characteristics to evaluate for when considering whether to evaluate for CD in patients who present with isolated perianal fistula; *courtesy of Serre-Yu Wong, MD, PhD.*

TOpClass consensus criteria for isolated perianal Crohn's disease
The following findings are sufficient for considering diagnosis of isolated perianal CD: • Histologically-confirmed disease: epithelioid granuloma in fistula or surrounding perianal tissue (excluding cryptolytic or foreign-body granulomas) • Crohn's perineum: anorectal stricture or inflammatory fissures or ulcers in the absence of another cause
Alternatively, consider isolated perianal Crohn's disease if score ≥5 based upon: **Major criteria** (3 points each): • Advanced fistula complexity • Family history of IBD in 1st or 2nd degree relative • Confirmed diagnosis of IBD-related extraintestinal manifestation or orofacial granulomatosis **Minor criteria** (1 point each): • Unconfirmed diagnosis of IBD-related extraintestinal manifestation (potential, past, or prior) • Suspected oral or genital CD • Presence of hidradenitis suppurativa • Minor perianal disease (single >1 cm edematous skin tag, ≥3 small skin tags, non-fistulizing perianal skin inflammation, or natal cleft ulceration) • Recurrence following fistula repair or lay-open procedure with curative intent

Table 2. TOpClass consensus criteria for isolated perianal Crohn's disease in patients presenting with perianal fistula and no luminal inflammation; *courtesy of Serre-Yu Wong, MD, PhD.*

evidence of inflammation that later manifested clinically and endoscopically as luminal CD. Other modalities that can be used include video capsule endoscopy, intestinal ultrasound, and magnetic resonance enterography.[15] Using a combination of these complementary tests may increase diagnostic yield, depending on the resources available at a given institution.[14]

Importantly, luminal disease may not be evident at initial presentation. In a case series from our institution, 25% of patients with isolated complex perianal fistulas developed luminal CD over time, with a median time to diagnosis of 2.5 years, and a range extending up to 10 years.[11] Therefore, a single negative evaluation should not be considered definitive. The TOpClass consortium emphasized the need for ongoing surveillance—though no consensus was reached on the optimal surveillance interval, with recommendations ranging from symptom-guided re-evaluation to routine annual screening.[14]

What if No Luminal CD is Found?

Between 5–10% of patients with PFCD will remain without evidence of luminal disease.[10,11] Historically, establishing a definitive diagnosis of isolated PFCD in such patients has not been clear. To address this gap, the international perianal disease TOpClass Consortium—a multidisciplinary panel of IBD gastroenterologists, surgeons, and radiologists—recently conducted

a systematic review and published consensus recommendations.[14] While not yet fully validated, these proposed diagnostic criteria offer practical guidance for clinical use (**Table 2**). According to these guidelines, the presence of diagnostic histopathologic features in fistula tissue or the surrounding area, as well as severe associated perianal disease, can independently establish a diagnosis of isolated PFCD. A total score of ≥5—achievable through either two major criteria, one major plus two minor criteria, or five minor criteria—is considered sufficient to support the diagnosis.

Effective diagnosis and management of isolated PFCD requires multidisciplinary collaboration. While gastroenterologists typically lead the evaluation for luminal disease, colorectal surgeons often have a clinical gestalt about whether a fistula's characteristics are more suggestive of CD rather than a cryptoglandular origin.

Managing Isolated PFCD

Shared-decision making is essential for managing isolated PFCD, and patients should be informed about both the knowns and unknowns of the disease. For patients experiencing significant perianal symptoms or whose fistulas are unlikely to heal with surgery alone, a trial of biologic therapy—typically anti-TNF agents—can be considered, provided the patient is amenable. Anti-TNFs may help reduce inflammation, support fistula healing, and facilitate surgical interventions.[16-18] However, it should be noted that the data supporting their efficacy is limited. One study, for example, reported lower remission rates in patients with complex idiopathic perianal fistula compared to those with confirmed PFCD.[19]

If a patient shows a positive response to optimized anti-TNF therapy, this treatment may be continued with regular monitoring. Yet, there is no consensus on the optimal treatment duration after clinical and radiologic remission—recommendations range from 3 months to lifelong therapy, reflecting the lack of data in this area. If there is no therapeutic response, anti-TNF therapy should be discontinued.[14] At that point, the diagnosis of isolated PFCD should be re-evaluated, and consideration given to initiating a second-line biologic.

Conclusion

Perianal fistulas without overt evidence of luminal CD present a clinical dilemma. While most are cryptoglandular in origin, a minority herald PFCD. Identifying these cases is important, as their medical and surgical management differs substantially from that for idiopathic fistulas. Comprehensive screening and luminal evaluation—including histology, imaging, and ongoing surveillance—are essential components of care. Yet, questions remain: Is isolated PFCD a distinct clinical entity? What constitutes the best treatment strategy? Further research is needed to clarify its natural history, guide treatment, and improve outcomes for this enigmatic subset of IBD.

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