Reviewer #1:
To diagnose and treat Crohn´s disease in infants can be very challenging. Ancona et al are describing a case of Crohn,s disease in a 5 months old infant and how they overcome the development of anti-drug antibodies to adalimumab by increasing the dose of the drug. It can be argued that the concept of restoring the effect of TNFalpha blockers in case of antidrug antibody development by increasing the drug dose is not new - at least not in "adult" gastroenterology. However I find the presented case interesting due to the severity of Crohn´s disease in infants and because it may be rather new knowledge for many pediatric gastroenterologists treating these patients. The case is very well presented and the language is excellent. I have in fact only a very few comments.

Thank you for your comments and for your suggestions. In particular:

- Introduction: It is stated that TDM has revolutionized the treatment with biologics. I would suggest to use a more modest term. It is correct that TDM can in some cases guide the treatment but the fact is that it has been rather difficult scientifically to prove the value of TDM in the proactive setting.

  "Revolutionized" could be interpreted such an assumptive term. However, TDM could guide anti-TNF treatment, especially in children because of their unpredictable pharmacokinetics. To maintain drug concentrations within an optimal targeted therapeutic window is essential in improving the efficacy of these medications. Indeed, ECCO-ESPGHAN guidelines suggest a proactive TDM, even if it is difficult to scientifically prove its value in the clinical practice.

- Further diagnostic work-up: I presume that the endoscopic examination was an ileocolonoscopy. This should be clarified (not just endoscopy assessment)

  We performed both an upper endoscopy and an ileocolonoscopy: the endoscopic findings described in the paragraph are related to the second one.

- Treatment: What are the standard dosis of adalimumab when treating infants? It may be known by pediatricians but it would be informative to other readers to add this information

  Adalimumab has been currently approved for the treatment of moderate-to-severe Crohn's Disease in children aged 6 years old or older. For patients with a weight > 40 kg, the drug label recommends a first induction dose of 160 mg (week 0), followed by 80 mg at week 2 and then a maintenance dose of 40 mg every two weeks. Instead, for patients < 40 kg, the therapy schedule recommended is 80 mg at week 0, followed by 40 mg at week 2 and 20 mg every two weeks (from week 4 onwards). However, ECCO-ESPGHAN guidelines suggest the possibility to use a higher dose in specific cases: for example, weekly injections should be considered in patients that experimented a loss of response or with low trough levels.

- Discussion: In the present case it was chosen to increase the dose of adalimumab to restore the effect of the drug. It would be informative in the discussion briefly to add

information as to what other treatment modalities could be considered (eg other biologics)

Instead of TDM-guided high dose ADA treatment, other therapeutic strategies could have been:

1) a combination therapy with an immunomodulator, such as azathioprine or methotrexate;
2) switching to another biologic drug, stopping ADA and starting, for example, ustekinumab or vedolizumab or infliximab (the last one was avoided for difficult venous accesses, but a more stable venous access could be arranged).

Reviewer #2:
This review presents a case study focused on the treatment of infantile-onset inflammatory bowel disease (IO-IBD), which often poses challenges due to its aggressive disease course and resistance to standard therapies, necessitating the use of biologic agents. A common issue encountered in patients with IBD receiving biologic treatment is the development of anti-drug antibodies, leading to secondary loss of response. The case study highlights the use of therapeutic drug monitoring (TDM)-guided high-dose anti-tumor necrosis factor (TNF) therapy as a strategy to address the presence of anti-drug antibodies. In this particular case, dose escalation monitoring was employed to overcome the inhibitory effects of anti-drug antibodies and optimize treatment efficacy. The utilization of TDM, a technique that involves measuring drug levels and anti-drug antibody titers in the patient's blood, allowed for personalized treatment adjustments based on individual pharmacokinetic and immunogenic profiles. By closely monitoring drug levels and the presence of anti-drug antibodies, the clinicians were able to guide dose escalation to achieve therapeutic drug concentrations and restore treatment response in the patient with IO-IBD.

Thank you for your kind comments.

Reviewer #3:
In this case report, Ancona et al described a case of infantile-onset IBD with Crohn's-like phenotype. The development of anti-adalimumab antibodies leading to a loss of response to ADA treatment was encountered early in the course of disease. By increasing the dose of ADA, the author and team managed to overcome the anti-ADA and rendered the infant in remission again. As the author stated, management of infantile-onset IBD often poses a therapeutic challenge. Successful management of IO-IBD with escalation of biologics offers pediatric IBD specialists an alternative way of managing this challenging condition. I have a few comments:

Thank you for your suggestions, in particular:

1. The authors described a successful strategy of overcoming ADA antibody. However, it remains to be seen whether in the medium-term future, a recurrence of ADA antibody may happen again. This needs to be emphasized in the Discussion.

Even if a stable clinical and biochemical remission was achieved for almost a year, a recurrence of ADA antibodies with a subsequent loss of response could happen again in the medium-term future. So, the clinicians could pay attention to this possibility, with a strict trough levels and antibodies monitoring, continuing to adjust adalimumab schedule therapy to trough levels, in order to overcome the antibody production.

2. Similarly, overcoming formation of ADA antibody leading to clinical response is a short-term strategy. Cognisant of the lack of consensus in the management of IO-IBD, especially in cases of IO-CD, the authors may like to speculate any exit strategy for this child or just maintaining the current strategy for the patient.

Other therapeutic strategies for our patients could have been:

1) Starting a combination therapy, adding an immunomodulator such as methotrexate or azathioprine;
2) Stopping ADA and trying another anti-TNF therapy, IFX; we have denied IFX because of difficult venous accesses, but a more stable venous access could be arranged by anesthesiologists (considering possible side effects correlated to CVC, as thrombotic events or infections);
3) Switching biologic drug, for example ustekinumab or vedolizumab

3. The whole exome sequencing result is awaiting. What is the likelihood of elucidating the genetic aspect of this case? If the result is expected to be available in the near future, it would make the manuscript more 'wholesome'.

IO-IBD, as our case, can underline a monogenic pathogenesis (for example primary immunodeficiencies). The diagnosis is important for the management of the patient, in particular for more targeted treatments as TCSE. The whole exome sequencing is now ongoing, so the result could be available in a very short time.

4. There are some minor issues with the English, which I am sure can be easily overcome by carefully vetting the manuscript again.

We have carefully vetted the manuscript again, so I hope that we have overcome these minor issues with the language.