ISSN(O): 2320-5407 | ISSN(P): 3107-4928
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

Manuscript No.: IJAR-57090

Title: Cyclic ACTH-Independent Cushing Syndrome in an Adolescent Revealing Multinodular Adrenal Hyperplasia: A Case Report,

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Recommendation:
Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality		✔,		
Techn. Quality		✔,		
Clarity	✔,			
Significance	✔,			

Reviewer Name: Dr.Bilqees Hamza

Detailed Reviewer's Report

The case report titled "Cyclic ACTH-Independent Cushing Syndrome in an Adolescent Revealing Multinodular Adrenal Hyperplasia" presents a significant clinical contribution to pediatric endocrinology. By detailing the diagnostic journey of an adolescent presenting with fluctuating hypercortisolism, the author highlights a rare and complex manifestation of adrenal disease. The paper effectively addresses the "diagnostic uncertainty" inherent in cyclic Cushing syndrome, where biochemical markers may return to baseline during quiescent phases, potentially leading to delayed intervention. The central value of this report lies in its meticulous documentation of the correlation between clinical observation, endocrine testing, and final histopathological confirmation, serving as a reminder that multinodular adrenal hyperplasia must remain on the differential for adolescents despite its rarity in this age group.

The primary strength of the manuscript is its clear clinical narrative, which follows the patient from the initial presentation of weight gain and striae to the definitive surgical resolution. The author's description of "alternating periods of hypercortisolism and partial or complete remission" provides a practical illustration of the challenges mentioned in the introduction. The inclusion of imaging findings that revealed a nodular radiological pattern, followed by the histopathological confirmation of multinodular hyperplasia, offers a complete "end-to-end" view of the case. This comprehensive approach is essential for case reports, as it allows clinicians to see the progression from a vague symptom set to a specific, unusual diagnosis.

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The paper's engagement with recent classifications of adrenal cortical proliferations is a notable academic merit. By placing this specific case within the "broader spectrum" of adrenal diseases, the author ensures the report is grounded in current medical consensus. The discussion on ACTH-independent versus ACTH-dependent forms in pediatric patients provides necessary context, correctly identifying that while ACTH-dependent forms are more common after early childhood, adrenal causes—especially bilateral nodular diseases—require high clinical suspicion when standard patterns do not align.

However, from a peer-review perspective, the manuscript could be enhanced with more detailed biochemical data. While the paper mentions "biochemical activity fluctuates over time," the inclusion of a table or a chronological graph showing the specific levels of urinary free cortisol (UFC), late-night salivary cortisol, and ACTH during both active and inactive phases would provide invaluable empirical weight. Quantifying these fluctuations would allow the reader to better understand the magnitude of the "cyclicity" and the potential for false-negative results during remission phases. This level of detail is critical for other endocrinologists who might be managing similar diagnostic dilemmas.

Furthermore, the discussion section could be expanded to explore the genetic implications of the diagnosis. Given the adolescent age and the bilateral nature of multinodular hyperplasia, a brief discussion on the potential role of genetic screening (e.g., for mutations in genes like *ARMC5* or *PRKAR1A*) would be highly appropriate. Modern endocrine management for such rare adrenal pathologies often includes genetic counseling, and addressing whether this was considered or performed for the patient would elevate the case report's relevance for genomic medicine.

Methodologically, the "careful and methodical approach" praised in the conclusion is well-represented in the text. However, the author should ensure that the "References" section is expanded. While the current references to *StatPearls* and *Frontiers in Endocrinology* are good starting points, the paper would benefit from citing seminal papers on cyclic Cushing syndrome and multinodular hyperplasia from the last five years (2021-2026) to demonstrate a command of the very latest clinical literature. Additionally, adding a specific section on the "Differential Diagnosis" explored during the "inactive phase" would provide a clearer pedagogical tool for medical students and residents.

The language of the case report is professional, precise, and highly readable. The author successfully maintains a balance between the specific clinical details of the patient and the broader educational takeaways for the medical community. To improve the narrative flow, the author might consider

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explicitly linking the histological findings back to the specific imaging anomalies noted earlier, reinforcing the "close correlation" mentioned in the summary.

In conclusion, "Cyclic ACTH-Independent Cushing Syndrome in an Adolescent" is a well-constructed and informative case report that fills a niche in the literature on pediatric adrenal disorders. It serves as a vital reminder of the "diagnostic challenge" posed by hormonal cyclicity and the importance of persistence in the face of inconsistent test results. With minor revisions to include more specific biochemical data and a brief discussion on genetic considerations, this manuscript will be a valuable addition to the clinical archives of any endocrinology or pediatric journal.

Recommendations:

1. Include a chronological table or graph detailing the specific fluctuations in cortisol and ACTH levels to provide empirical evidence of the disease's cyclicity.
2. Add a discussion on the relevance of genetic testing for adolescents with bilateral multinodular adrenal hyperplasia, addressing whether screening for germline mutations was considered.
3. Expand the "Differential Diagnosis" section to specifically explain how the team ruled out other causes of cyclic symptoms during the patient's quiescent periods.
4. Update the bibliography to include more primary research articles and systematic reviews from 2022-2026 regarding cyclic Cushing syndrome.
5. Ensure that all radiological and histopathological images (if included in the final version) are clearly labeled with the specific features that led to the diagnosis of multinodular hyperplasia.
6. Refine the conclusion to offer a brief "Practice Point" or "Clinical Pearl" for general pediatricians who might encounter early, fluctuating symptoms of hypercortisolism.

Recommendation: Recommend for publication with minor revision.