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Case Series

Comparative analysis of clinicopathologic features between adenoma and hyperplasia in surgically treated patients for hyperparathyroidism: A retrospective study

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ABSTRACT

Background: Hyperparathyroidism (HPT) is a common endocrine disorder resulting from overproduction of parathyroid hormone (PTH). Usually HPT is caused by parathyroid adenoma (PA) or parathyroid hyperplasia (PH). Our aim is to assess clinicopathologic features associated with PA and PH in patients with HPT.

Methods: We retrospectively collected 29 cases of HPT recorded at the Department of Pathology of Hassan II University Hospital of Fes, Morocco, from 2013 to 2016.

Results: The mean age was 52.14 ± 15.7 years (range of 22–76 years), 13 patients (44.8%) had primary HPT, 16 (55.2%) had secondary HPT. The largest size of the resected parathyroid specimens ranged from 1 to 3.6 cm (mean of 2.26 ± 0.66 cm). Seventeen patients (58.6%) had PA, the remaining cases were diagnosed as PH. There were no significant statistical differences between PA and PH in age, sex, clinical presentation, preoperative serum PTH, or in parathyroid gland size ($P > 0.05$). However compared to PH, PA is more often a single-gland disease, found in primary HPT with higher preoperative calcium level ($P < 0.05$).

Conclusions: In patients surgically treated for HPT, PA is associated with some distinctive clinicopathologic features. These findings could be helpful to pathologists and clinicians for appropriate clinicopathologic management.

1. Introduction

Hyperparathyroidism (HPT) is a common endocrine disorder resulting from overproduction of parathyroid hormone (PTH) by parathyroid glands [1,2]. Overproduction of PTH may be a consequence of hypocalcemia, hyperphosphatemia (secondary HPT) or may be a result of autonomous parathyroid glands hyperfunction in the absence of a known stimulus (primary HPT) [3]. Primary HPT (pHPT) is associated with hypercalcemia, it is often a sporadic disease with about 5% cases resulting from hereditary syndromes (multiple endocrine neoplasia syndromes (MEN), hyperparathyroidism-jaw tumor, familial hypocalciuric hypercalcaemia, familial hypercalciuric hypercalcaemia or isolated familial HPT) [1]. On the other hand, secondary HPT (sHPT) is a consequence of PTH hypersecretion in response to metabolic disorders (hypocalcemia, hyperphosphatemia, low serum vitamin D) often found in chronic renal failure [3–5]. Tertiary HPT is defined as autonomous parathyroid hyperfunction in a background of sHPT [3]. The clinical symptoms of HPT vary widely from asymptomatic to urinary tract stones, bone demineralisation, bone fracture, fatigue or headach [1–3]. Histologically, patients with HPT present with parathyroid adenoma (PA), parathyroid hyperplasia (PH) or very rarely with parathyroid carcinoma [1,6]. Parathyroid adenoma is a clonal disease and affects usually one gland whereas PH is often a polyclonal disease and affects all parathyroid glands [6–8]. As a consequence, the surgical treatment of PA consists of a minimally invasive approach whereas PH requires more invasive surgical approach [6–10]. Adenoma is more frequent in

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patients with pHPT while PH is often found in patients with sHPT, however PA or PH could be encountered in both pHPT and sHPT [1–3, 6].

The objective of our current study is to assess clinical, biochemical and histologic features associated with PA and PH in patients with hyperparathyroidism. The knowledge of these features would lead clinicians to better select patients for appropriate surgical management. This work has been reported in line with the PROCESS 2020 criteria [11].

2. Methods

2.1. Patients selection

This was a retrospective study including 29 consecutive patients with HPT (primary or secondary HPT) recorded at the Department of Pathology of Hassan II University Hospital of Fes, Morocco, from 2013 to 2016. Available clinical, biochemical and pathologic data were collected from patients'request forms, pathology records and the patients' medical online records. Preoperative neck ultrasound and technetium-99m-sestamibi scan (Fig. 1) were performed in all cases. All patients underwent surgical resection and were successfully treated with minimum follow-up of 3 months post-operatively. Patients with incomplete data were excluded from the study (3 patients excluded for incomplete data).

2.2. Histopathologic analysis

The histologic analysis was performed on formalin fixed and paraffin-embedded tissue sections with hematoxylin-eosin staining (H&E). The diagnosis of PA and PH were made in accordance with previously described histologic criteria: presence or absence of capsule, presence or absence of fat cells, coexistence with normal parathyroid tissue, cell types in the lesion [12,13].

2.3. Statistics

Patients were divided into 2 groups: PA group and PH group. Differences in the distribution of variables between the 2 groups were assessed using the Fisher exact test or chi-square test (for categorical variables) and Student's t-test (for non-categorical variables). Results were considered statistically significant when $P < 0.05$. Data are presented as mean ± SD (standard deviation) or as number (percentage).

This study was registered in the research registry with UIN researchregistry7124 (link: https://www.researchregistry.com/browse-the-registry#home/)

3. Results

We have recorded 29 patients surgically treated for HPT, the mean age was 52.14 ± 15.7 years (range of 22–76 years), 18 patients (62.1%) had ≥50 years (Table 1). Females were predominantly affected (22 cases, 75.9%). Osteoarticular symptoms (bone pain, osteoporosis, or bone fracture) were present in 23 cases (79.3%), 4 patients (13.8%) had recurrent kidney stones. Concomitant thyroid gland hyperplasia was

Table 1
Clinicopathologic features of patients with hyperparathyroidism.

	Number	Percentage (%)
Sex		
- Males	7	24.1
- Females	22	75.9
Age		
- Mean ± SD	52.14 ± 15.7	–
- < 50 years	11	37.9
- ≥ 50 years	18	62.1
Clinical symptoms		
- Urinary tract	4	13.8
- Osteoarticular	23	79.3
- Both	2	6.9
HPT cause		
- Primary	13	44.8
- Secondary	16	55.2
Thyroid gland hyperplasia		
- Absent	18	62.1
- Present	11	37.9
Nb of glands		
- 1 gland	13	44.8
- > 1 gland	16	55.2
Localisation		
- Eutopic gland	26	89.7
- Ectopic gland	3	10.3
Gland size (largest)		
- Mean ± SD	2.26 ± 0.66	–
- < 3 cm	22	75.9
- ≥ 3 cm	7	24.1
Histologic lesion		
- Adenoma	17	58.6
- Hyperplasia	12	41.4
Cellular type (predominant)		
- Chief cells	23	79.3
- Clear cells	6	20.7
Biochemistry		
- PTH (Mean ± SD) (pg/mL)	1276.59 ± 761.757	–
- Calcium (Mean ± SD) (mg/L)	114.35 ± 18.22	–

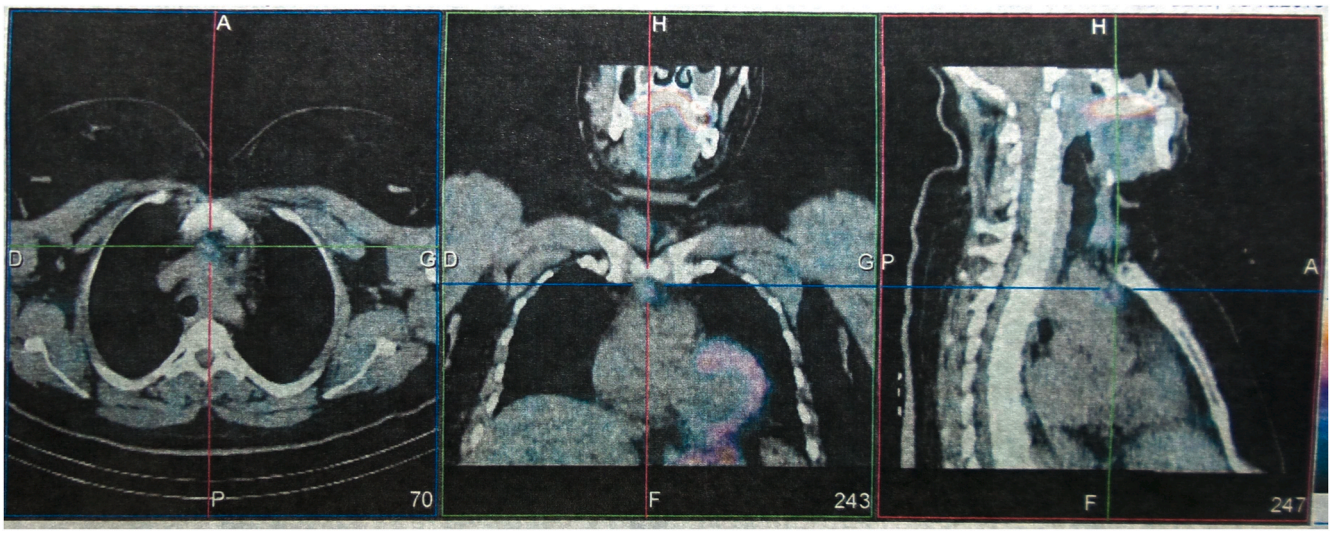

Fig. 1. Sestamibi scan in a patient with primary hyperparathyroidism showing anterior mediastinal hyperfixation due to ectopic parathyroid adenoma.

present in 11 patients (37.9%). Thirteen patients (44.8%) had pHPT with one case of MEN type 2A; 16 patients (55.2%) had sHPT with chronic renal failure. Mean preoperative PTH was 1276.59 ± 761.757 pg/mL (range of 93.6–2558.89 pg/mL), mean preoperative serum calcium was 114.35 ± 18.22 mg/L (range of 86–153 mg/L).

Most patients had eutopic parathyroid glands (26 cases, 89.7%), 3 patients (10.3%) had ectopic parathyroid glands (2 cases with intrathymic location and 1 case with intrathyroid location). Sixteen patients (55.2%) had multiglandular disease (double PA or PH). The largest size of the resected parathyroid specimens ranged from 1 to 3.6 cm (mean of 2.26 ± 0.66 cm) (Fig. 2A, B, 2C). At histologic analysis, 17 patients (58.6%) had PA (Fig. 3A), the remaining cases were diagnosed as PH (Fig. 3B). Chief cell-type lesions were the predominant histologic variant in both PA and PH, with rare clear cell-type lesions. All 3 ectopic lesions were PA embedded in the thyroid gland or in the thymus.

There were no significant statistical differences between PA and PH in age, sex, clinical presentation, in thyroid gland status or in lesion cellular type ($P > 0.05$) (Table 2). Also, gland size is not significantly different between these 2 histologic entities (mean of 2.27 ± 0.66 cm for PA and 2.24 ± 0.682 cm for PH; $P = 0.910$). Parathyroid adenoma (PA) is usually a monoglandular disease (13 cases, 76.5%) and PH is always a multiglandular disorder ($P < 0.001$). In fact all cases of PH are multiglandular, while 4 patients (23.5%) had double PA. Parathyroid adenoma (PA) is more frequent in patients with pHPT (11 cases, 64.7%) whereas PH is more found in patients with sHPT (10 cases, 83.3%) ($P = 0.022$). Only 2 patients (16.7%) with sHPT had PA. Also, there was a significant statistical difference between patients with PA and PH in serum calcium (mean of 121.16 ± 19.642 mg/L for PA, 104.69 ± 10.535 mg/L for PH; $P = 0.014$). Patients with PA had lower level of serum PTH than those with PH, however the difference was not significant ($P = 0.127$).

4. Discussion

Through our current retrospective study, we have tried to find distinctive clinical, biochemical and histopathologic characteristics between PA and PH in patients with HPT whether primary or not. Parathyroid adenoma or hyperplasia could be found in primary HPT (pHPT) or in secondary HPT (sHPT) with variable incidences [1–3]. As these 2 histologic entities (PA and PH) could be found in pHPT or sHPT, we find logic to include patients with both type of HPT although many authors used to report separately patients with pHPT or sHPT [5,7,12,14–18]. Patients with secondary hyperparathyroidism by definition have diffuse hyperplasia as it is a secondary process stimulating all of the glands. If patients with secondary hyperparathyroidism develops an adenoma, then they have primary and secondary hyperparathyroidism. Occasionally patients with long standing secondary hyperparathyroidism can develop autonomous nodules within their background of hyperplasia and convert to tertiary hyperparathyroidism. The clinical features of our patients are quite similar to those in previous reports, with a mean age around 50 years and a marked female predominance [16,17,19]. All patients of our cohort were symptomatic with osteoarticular symptoms (79.3%, n = 23, with 4 cases of bone fracture), urinary lithiases (13.8%, n = 4) or with both osteoarticular and urinary tract symptoms (6.9%, n = 2). In our study, there were no significant differences in age, sex and clinical presentation between patients with PA and PH ($P > 0.05$). Previously, some authors have reported asymptomatic patients with HPT, and symptoms had been linked to the duration of the disease [14,17].

In our study, 16 patients (55.2%) had sHPT due to chronic renal failure, and the remaining cases (n = 13, 44.8%) had pHPT with 1 case of MEN type 2A. Parathyroid adenoma was mostly diagnosed in patients with pHPT (64.7%, n = 11), whereas PH was more frequent in patients with sHPT (83.3%, n = 10), ($P = 0.022$). As a consequence, serum calcium level was higher in patients with PA than those with PH (respective means of 121.16 ± 19.642 mg/L and 104.69 ± 10.535 mg/L, $P = 0.014$). Patients with PH had higher serum PTH level than patients with PA, however the difference was not statistically significant ($P = 0.127$). As most cases of PH were encountered in sHPT (hypocalcemic disorder), it seems normal to find lower serum calcium level in these patients when compared to PA that was more often diagnosed in patients with pHPT. In the literature, data including patients with pHPT and sHPT are very scarce [19,20]. As in our study, it is well established that PA is more frenquently associated with pHPT while PH is more frequent in sHPT [1–3]. In patients with pHPT, there were conflicting data between PA (often a single-gland disease) and PH (multigland-disease) in regard to preoperative serum calcium and PTH [7,8,15]. We have found that in patients with HPT, PA is usually a single-gland disease (76.5%, n = 13; $P < 0.001$), and there was no significant difference between PA and PH in size (respective mean size of 2.27 ± 0.666 cm and 2.24 ± 0.682 cm; $P = 0.910$), unfortunately we have no data about specimens' weight. In their study on 260 cases of pHPT Sun. et al. found no statistical difference in parathyroid gland size between patients with PA and PH, however they found that parathyroid carcinoma had higher size than PA and PH [17].

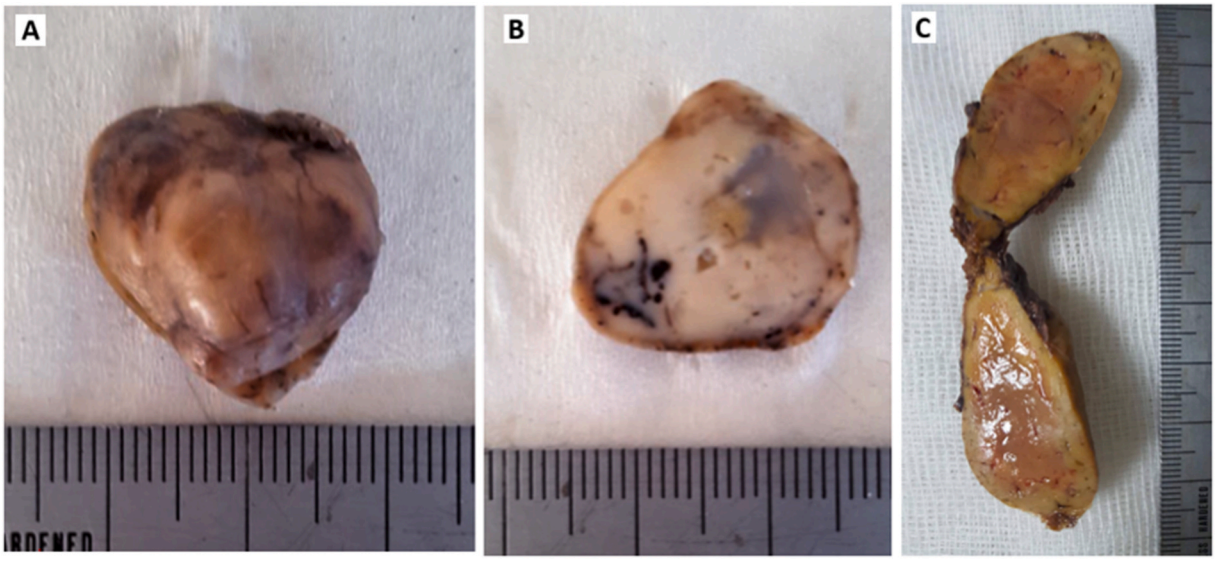

Fig. 2. Macroscopic view of a case of parathyroid adenoma showing a well-encapsulated nodule (A). The cut surface shows grayish lesion with microcystic and hemorrhagic changes (B). Macroscopic view of a case of parathyroid hyperplasia. The cut surface shows enlarged gland with yellowish and homogenous aspect (C).

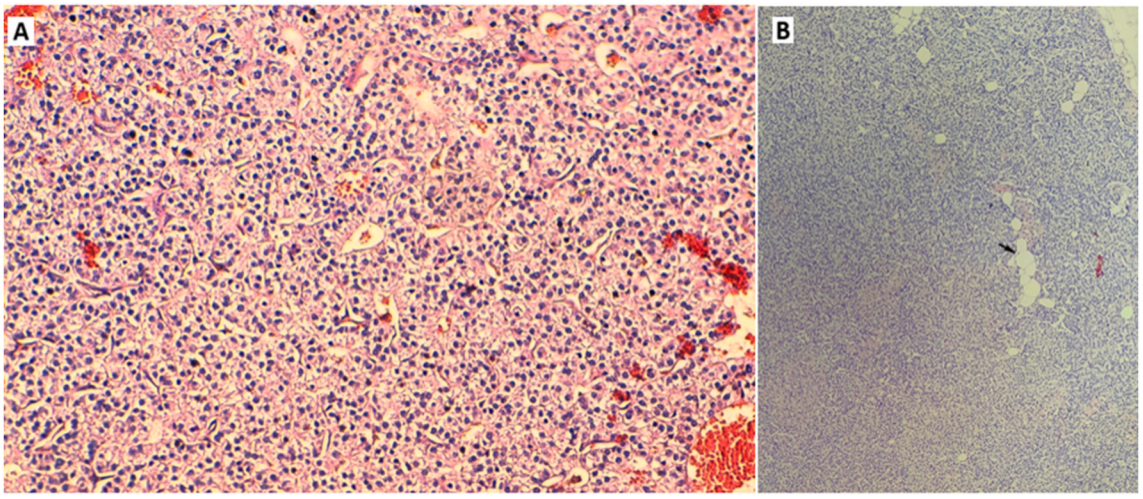

Fig. 3. Histologic image of parathyroid adenoma consisting of polygonal chief cells with eosinophilic granular cytoplasm and oval nuclei. Cells are arranged in cords and trabeculae with a rich branched vasculature, (Hematoxylin-eosin x 200) (A). Histologic view of parathyroid hyperplasia showing a densely cellular gland with some persistent fat cells (arrow), (Hematoxylin-eosin x 50) (B).

Table 2
Comparison of clinicopathologic features between adenoma and hyperplasia in patients with hyperparathyroidism.

	Adenoma (n = 17)	Hyperplasia (n = 12)	*P* value
Sex			
- Males (n = 7)	4 (23.5%)	3 (25%)	1.000
- Females (n = 22)	13 (76.5%)	9 (75%)	
Age			
- Mean ± SD	53.88 ± 16.697	49.67 ± 14.512	0.486
- < 50 years (n = 11)	6 (35.3%)	5 (41.7%)	0.514
- ≥ 50 years (n = 18)	11 (64.7%)	7 (58.3%)	
Clinical symptoms			
- Osteoarticular (n = 23)	12 (70.6%)	11 (91.7%)	0.502
- Urinary tract (n = 4)	3 (17.6%)	1 (8.3%)	
- Both (n = 2)	2 (11.8)	0 (0%)	
HPT cause			
- Primary (n = 13)	11 (64.7%)	2 (16.7%)	**0.022**
- Secondary (n = 16)	6 (35.3%)	10 (83.3%)	
Thyroid gland hyperplasia			
- Absent (n = 18)	12 (70.6%)	6 (50%)	0.438
- Present (n = 11)	5 (29.4%)	6 (50%)	
Nb of glands			
- 1 gland (n = 13)	13 (76.5%)	0 (0%)	**< 0.001**
- > 1 gland (n = 16)	4 (23.5%)	12 (100%)	
Gland size (largest)			
- Mean ± SD	2.27 ± 0.666	2.24 ± 0.682	0.910
- < 3 cm (n = 22)	13 (76.5%)	9 (75%)	1.000
- ≥ 3 cm (n = 7)	4 (23.5%)	3 (25%)	
Cellular type (predominant)			
- Chief cells (n = 23)	13 (76.5%)	10 (83.3%)	1.000
- Clear cells (n = 6)	4 (23.5%)	2 (16.7%)	
Biochemistry			
- PTH (Mean ± SD) (pg/mL)	1094.22 ± 799.604	1534.95 ± 650.275	0.127
- Calcium (Mean ± SD) (mg/L)	121.16 ± 19.642	104.69 ± 10.535	**0.014**

Recently McHenry et al. reported that PH should be suspected in patients with lower gland weights and negative imaging [8], however some authors did not find significant difference in parathyroid gland size between patients with PA and PH [10]. Ectopia in HPT is very rare [2,3]; we have recorded 3 cases (10.3%) of ectopic PA in the thymus and thyroid gland. Ectopic thymic PA have been removed through thoracotomy by thoracic surgeons.

Histologically, chief cells are the most common cellular type in both PA and PH, clear cell lesions are very rare [2,3]. We have found 4 cases of clear cell PA (23.5%) and 2 cases of clear cell hyperplasia (16.7%), ($P = 1.000$). It is important to remember that the distinction between PA and PH is not always easy even histologically, the concordance rate between pathologists was poor in one reported study [13]. This challenging diagnostic issue seems to justify the histological diagnosis of PA in some patients with sHPT in our sample, this seems to be aberrant in a clinical point of view. However, overall our study finds that PA is more frequent in patients pHPT ($P = 0,022$), confirming what is commonly reported in the literature.

Parathyroid adenoma is classically a well-circumscribed tumor replacing the normal parathyroid gland that is usually found at the periphery of the lesion, and fat cells are absent unlike PH [1–3,12,13].

As PA is more often a single-gland disease and PH a multigland disease, the surgical management of PA is ideally a focused mini-invasive approach [7,8,15,21]. Thus, the preoperative distinction between PA and PH is a very important issue for surgeons. Imaging techniques are not always helpful especially in patients with PH, the quick intraoperative parathyroid hormone assay (qPTH) seems to be a very effective tool in the surgical management of hyperparathyroidism [8,9]. Parathyroidectomy is associated with a more than 95% cure rate, however cases of recurrent or persistent HPT have been reported and reoperations of these patients have been linked to initially missed hyperfunctioning gland either in eutopic or ectopic location [16,19]. In our study 11 patients (37.9%) had concomitant thyroid gland abnormality (hyperplasia) with 5 cases (29.4%) associated with PA and 6 cases (50%) in patients with PH, ($P = 0.438$). These findings have also been reported in the literature emphasizing the necessity to check for thyroid gland status in all patients with HPT [22,23].

Although our study presents a particular characteristic of comparing PA and PH in patients with HPT either primary or secondary, the retrospective monocentric nature and the small patients number are non negligeable limitations. Large prospective studies including both patients with pHPT and sHPT are needed in order to draw more robust conclusions.

5. Conclusion

In patients surgically treated for hyperparathyroidism (HPT), unlike parathyroid hyperplasia (PH) parathyroid adenoma (PA) is a single-gland disease frequently associated with primary hyperparathyroidism (pHPT). These findings could be helpful to pathologists and clinicians for appropriate histopathologic diagnosis and clinical management.

Ethical approval

As a retrospective study and as data had been de-identified ethical approval is not required in our institution (not applicable).

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This study has not received any funding.

Author contribution

BE, wrote the article and made substantial contributions to conception and design of the article; RS, LT, MS, KM, and AO have been involved in drafting the manuscript and revising it critically for important intellectual content. LC has been involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final version of the manuscript.

Consent

Not applicable.

Registration of research studies

1. Name of the registry: This study was registered in the research registry with UIN researchregistry7124.
2. Unique Identifying number or registration ID: researchregistry7124.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/

Guarantor

Boubacar Efared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

All authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102929.

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