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Paraneoplastic Nephrotic Syndrome in Breast Cancer HCV Positive- A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author GA provided the case, the figures, managed literature searches and supervised the work. Author SD wrote the draft of the manuscript and designed the figures. Authors II and BD managed the literature searches and contributed to the correction of the draft. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Our aim was to illustrate a case of Membranous Glomerulopathy (MG), which is the commonest paraneoplastic pathology associated with the nephrotic syndrome, and develops in parallel with salient/ unapparent cancer evolution phases.
Presentation of Case: We present a rare case of a 39-year-old female patient with nephrotic syndrome considered secondary to a Hepatitis C with elevated viremia and to a breast cancer (BC), which was lately revealed by Ductal Echography (DE) and confirmed by Mammography and fine-needle aspiration biopsy, with BC staged T4NxMx.
Discussion: The nephrotic syndrome is usually considered as idiopathic, at least in the initial stage. Some other diseases may be incriminated as etiological factors in the secondary nephrotic syndrome, with simultaneous evolution and improvement/healing of the nephrotic impairment after the removing of the associated disease.
Conclusion: The paraneoplastic nephrotic syndrome associated to BC is a rare condition, and the

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best cost-efficient method of diagnosis could be the anatomical technique of Ultrasonography / DE, which is not operator dependent and allows the accurate detection of breast malignancy, suitable in earlier stages. Otherwise, some cases are missed or diagnosed in advanced stages, such in this presentation.

Keywords: Membranous glomerulopathy; secondary nephrotic syndrome; breast cancer; ductal echography.

1. CASE REPORT

We report the case of a nephrotic syndrome initially considered idiopathic for a year, before the precise cause was established.

History revealed a patient of 39 year-old, who had undergone hysterectomy prior 2 years for uterine leiomyofibromatosis, followed by a nephrotic syndrome developed in the last year. As associated pathology a chronic liver disease with HCV antigenic viremia of 2837UI/ml was identified prior 3 months to the actual admission, and interferon treatment was recommended (the patient's medical record in study for treatment approval). The patient's complaints were marked asthenia, dizziness, syncope, anxiety and lower limbs swelling.

A kidney biopsy in other service 3 months before the actual admission established the diagnosis of Membranous Glomerulopathy (MG). Despite the treatment based on low-protein and low-salt diet, diuretics and anticoagulants, the evolution was worsening.

The actual admission revealed at the clinical examination: general bad condition, pale skin and mucosa, lower limbs edema up to the groin region, distended abdomen apparently by increased subcutaneous fatty tissue; the blood pressure measured 80/50 mm Hg, the heart rate 90/min; the urine output up to 1500 mL / 24 h.

The laboratory studies revealed a moderate anemia with hemoglobin of 11.4 g%, hematocrit 34.3% (range 38%-46%), normal WBC 8,700/mmc, upper limits urea 21 mg/dL (normal 6-20 mg/dL), normal creatinine 0.58 mg/dL (range o.4-1.1 mg/dL), but elevated proteinuria of 26 g / 24 h with urine cultures negative and pathological serum electrophoresis: total protein 3.9%, albumin 19.5%, α1=2%, α2=39.7%, β1=10.4%, β2=12.4% and γ=16%. The erythrocyte sedimentation rate, despite no more valued in practice, was very high of 90/130 mm (normal less 13 mm at 1 hour and less 20 mm at 2 hours in females).

A posterior-anterior chest X-Ray (plain film) suggested pleurodesis of the left pleural sinus and normal cardiac silhouette.

We performed a general Ultrasonography that demonstrated:

- Pleural effusion in the great right pleural cavity estimated over 600 ml, and in the left pleural cavity over 150 ml (Fig. 1); the thoracic Ultrasonography is easy to perform and has the best results for the pleural and subpleural findings upon Lichtenstein [1]. A retrospective diagnosis justified the misdiagnosis of the fluid by the chest X-Ray, because of the high position of the diaphragm and of the mammary shadows projected at the bases of the thorax view;
- Large amount of fluid in the submezocolic space of the peritoneal cavity, without extension in the sub diaphragmatic space, paracolic sulci and in the Morrison space;
- Edema of the lower limbs, up to the groin regions, extended to the lower abdominal wall, without any thrombosis or flux inversion in the inferior vena cava, iliac veins and deep lower limbs veins;
- Left breast Ultrasonography demonstrated normal findings; the right breast presented edema more intense in the lower quadrants, clinically misinterpreted as sign included in the edematous nephrogenic disease, but with acute inflammatory aspect (hyperthermia and hyperemia) (Fig. 2). The Doppler Ductal Echography (DE) upon Teboul [2], which is performed in the radial and antiradial axes of the mammary lobes, following the main ducts and their connections, illustrated edema concerning the skin, the premammary fatty tissue and the mammary lobar structures, mostly in the lower quadrants of the right breast, with salient diffuse vasculature (Fig. 3).

In the upper-outer quadrant DE identified a mass over 3 cm diameter, hypoechoic, with acoustic shadowing and spiculated borders, extended

through the Cooper ligaments towards the skin and the pectoral fascia (Fig. 4); the DE allowed the demonstration of ductal connection to the mass, which is a proof of the breast parenchymal tumor origin; the emerging centripetal ducts were thickened with fluid contents, representing paraneoplastic duct ectasia (Fig. 5).

The multipolar tumoral vasculature had an incident plunging angle of malignant type [3] (Fig. 4). Power Doppler illustrates the multipolar incident angle of the plunging artery of breast tumor, with high positive predicting value for malignant lesions [3].

The axillary lymph nodes (Fig. 6) were enlarged with the transverse axe up to 13 mm, but with normal thin cortical structure, hypoechoic central area and normal vasculature in the hilum, interpreted as reactive lymph nodes. The overall breast findings were assessed US BI-RADS 5 category.

Right breast fine needle aspiration biopsy (FNAB) obtained hypercellular smear, with many areas of epithelial ductal cells presenting moderate nuclear atypia, frequent nude nuclei, dyskaryosis, and small fragments of fibro-conjunctive tissue, frequent lymphocytes and erythrocytes; the test was considered positive for the breast lump. The patient underwent a Mammography that demonstrated a diffuse increasing of the right breast density and skin thickening of edematous aspect.

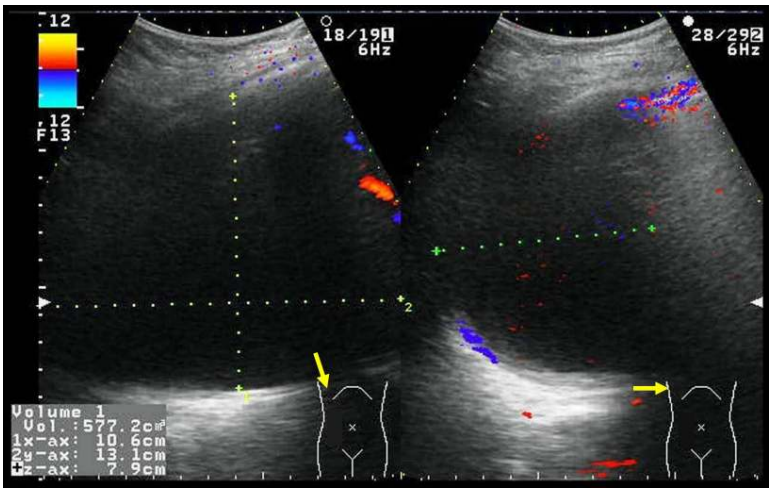

Fig. 1. Right pleural effusion volume estimated by ultrasonography in the longitudinal and transverse scans, performed on the right medial axillary line upon Lichtenstein [1]

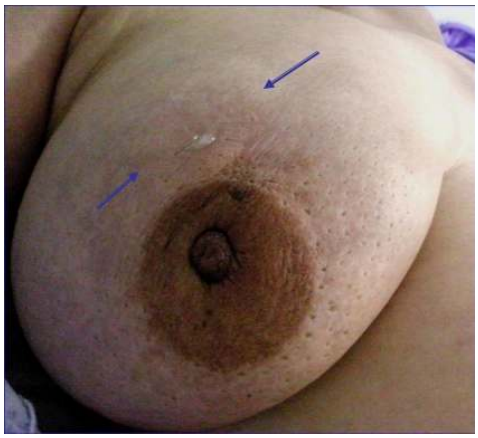

Fig. 2. Right breast edema with "orange peel skin sign" more visible in the lower quadrants and a visible lump in the upper-outer quadrant

In the right upper-outer quadrant was detected a mass of 45X35X23 mm, with spiculated borders, an inhomogeneous dense center, with pulverulent microcalcifications projected intra and perilesional and nipple retraction; presence of right axillary lymph nodes with abnormal architecture and up to 13.7 mm diameter (interpreted by independent radiologist as the greatest radiological diameter).

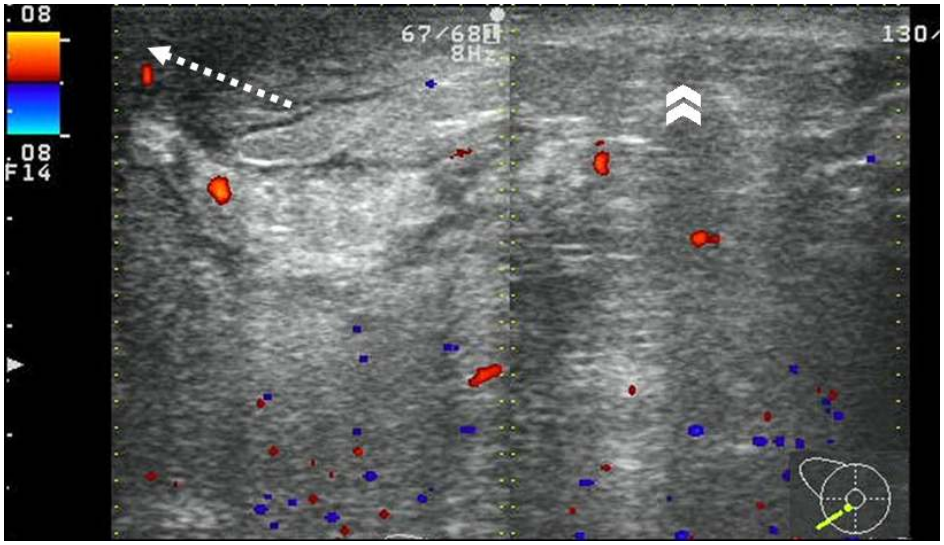

Fig. 3. Corresponding aspect of breast edema in ultrasonography: DE at R: 8:00 illustrates diffuse increasing of the echogenicity of the skin and of the premammary fatty tissue («) with loss of the differentiation with the glandular hyperechoic stroma, thickening of the areolar skin, diffuse moderate increasing of the vasculature in Doppler research (nipple and areola standardized location in the left-upper corner of the screen - squared dot arrow)

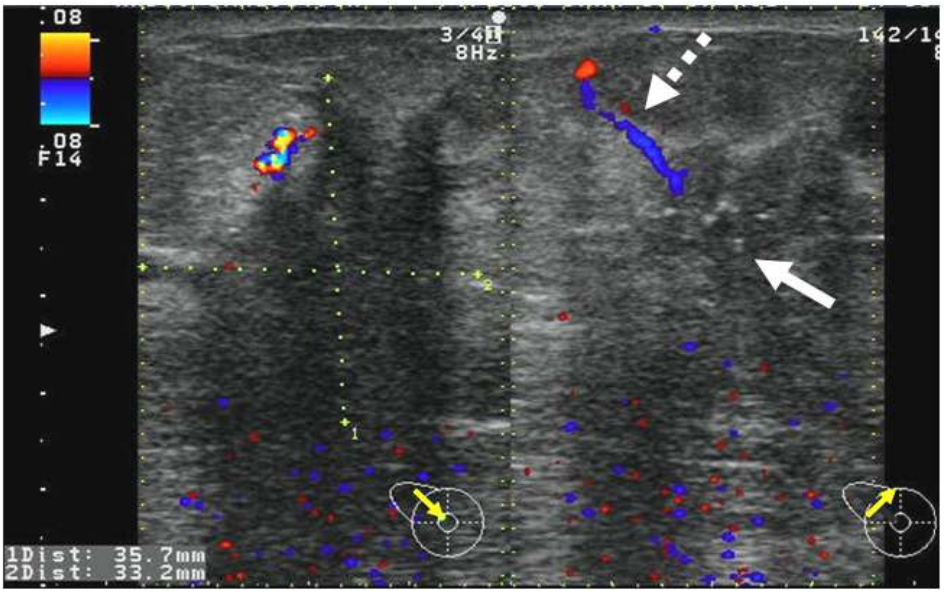

Fig. 4. DE of the R-breast: 10:30 radial and antiradial scans illustrate the hypoechoic mass with spiculated borders and halo sign, suspected microcalcifications (white solid arrow), incident angle of the plunging artery (square dot arrow), acoustic shadow, thickening of the Cooper ligaments and loss of delineation with the pectoral fascia

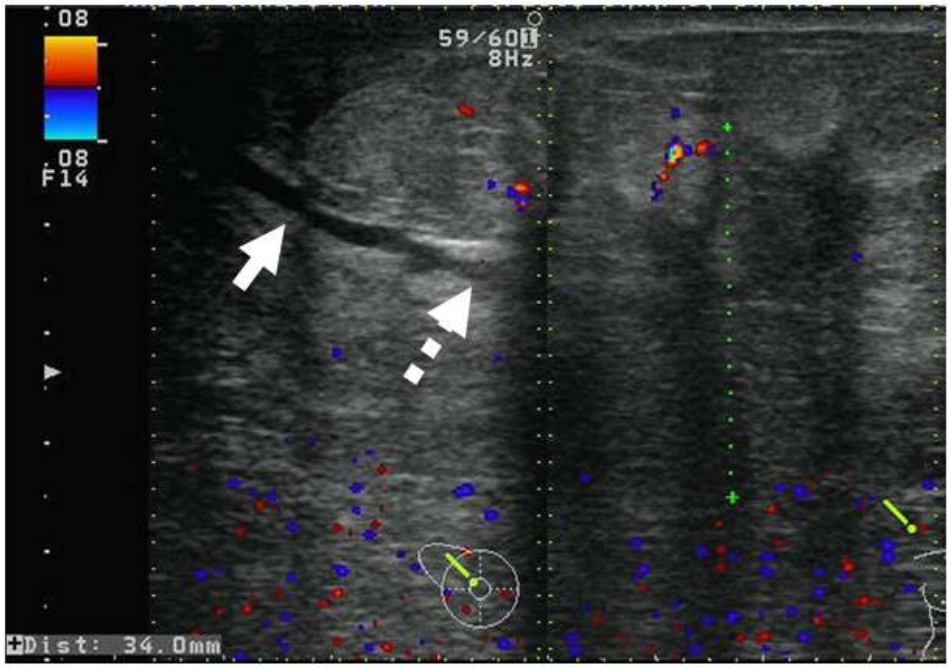

Fig. 5. DE of the R-breast: 10:30 radial scan illustrates the connection of the tumor (between calipers) with the nipple by a thickened duct, which is fluid-filled in the retroareolar segment with transonic aspect (solid arrow), and has a dense content in the peripheral segment, isoechoic with the tumoral structure, suggesting the intraductal tumoral extension (square dot arrow)

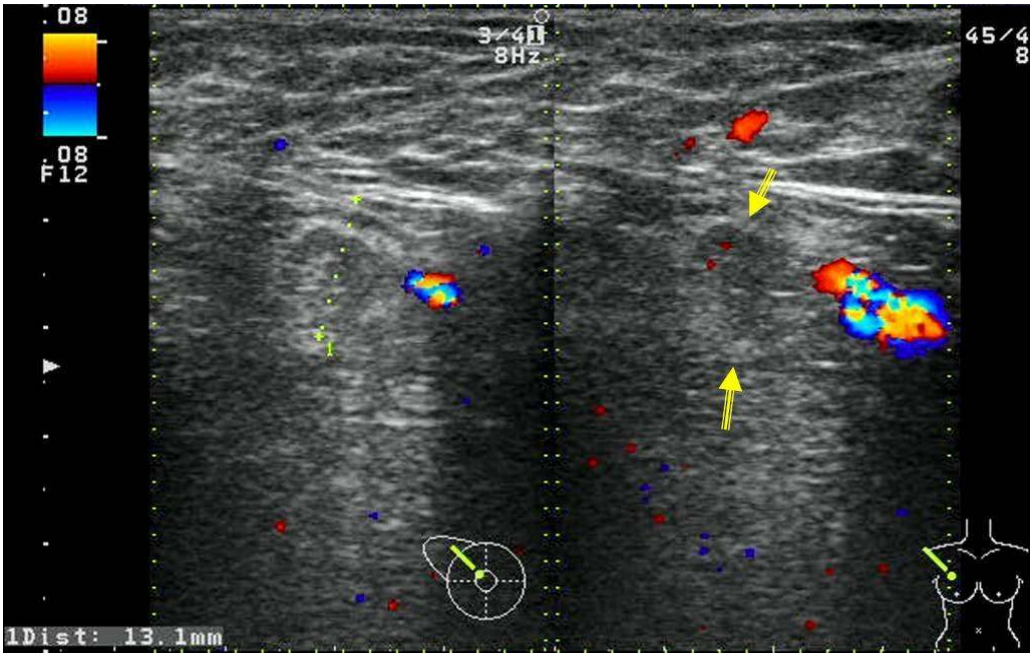

Fig. 6. Enlarged axillary lymph nodes with thin cortical structure, hypoechoic central area of the sinus and no salient pericapsular and cortical vasculature (usually present in metastatic lymph nodes) - aspect of benign adenomegalies type reactive lymph nodes

Axillary lymph nodes aspirate was negative for cancer.

The support medication with intravenous infusions with Albunorm (Albuminum humanum), diuretics (Furosemidum), anticoagulants (Acenocumarolum) and anti gastric secretor (Pantoprazolum) did moderate improvement of the general condition, with blood pressure of 90/60 mmHg, pulse of 80/min, constant urine output up to 1500 mL / 24 h.

The surgical treatment of the BC was delayed after first-intention oncological treatment, the patient being assessed stage T4bNxMx.

2. DISCUSSION

MG represents the most common cause that determines the Nephrotic Syndrome in adults. MG is caused by the immune complexes that built-up in the kidney, resulting a thickening of the vessel walls within the kidney filters. In this case the protein electrophoresis demonstrated low level serum albumin and elevated α2, β1 and β2 globulins, concordant with proteinuria.

The etiology of the MG may be either unknown in Primary / Idiopathic MG, or Secondary, when there is a relationship with other diseases, the most common being the autoimmune diseases (Systemic Lupus Erythematosus, Rheumatoid arthritis, etc), infections (Hepatitis B and C, malaria, schistosomiasis, TB, and leprosy, syphilis, mostly in developing countries [4]), cancers (lung, colon, breast), drugs (Penicillamine, gold, non-steroid anti-inflammatory drugs), and so on.

The paraneoplastic nephropathy/glomerulopathy refers to a glomerular disease without specific etiology, which develops in parallel with either salient or unapparent cancer evolution phases (improvement, remission, recurrence) [5]; there is no specific pathological or biological tests to discriminate the Primary MG from the Secondary type, but a routine age-appropriated cancer screening is mandatory. The most common neoplasias associated with paraneoplastic MG are Hodgkin's lymphomas, lung and gastrointestinal tract carcinomas, and rarely was found BC [5,6].

The differential diagnosis of the paraneoplastic glomerulopathy must include the irreversible renal injuries induced by the oncological treatment, such as Pamidronate treatment in advanced BC [7]; in those cases, the glomerulopathy associated with tubular-interstitial damage determine irreversible renal failure that does not improve after discontinuation of the treatment.

The prevalence of the disease is found in adults older than forty, more often in men, commonly in whites. The particularity of this case is a younger female patient, with previous gynecological pathologic history.

In a study from 2005 of Rihova and al, 40/129 cases with MG had primary cause verified: the disease was drug induced in 18 patients (45%), 11 patients (27.5%) had autoimmune disease, solid tumors were present in seven patients (17.5%), hepatitis B in three patients (7.5%), and one patient was diagnosed with both hepatitis B and prostate carcinoma [8].

Breast cancer associated with MG was found as rare as up to 7% by Leeaphorn et al. [9] which published in 2014 a systematic review of the literature and made a meta-analysis, but some cases were excluded (case reports, case series, cross-sectional studies, studies with uncertain follow-up adherence, studies that limited the population age, studies that did not specify the types of tumor, and studies that demonstrated incidence of cancer only after the time of diagnosis of MG).

The BC in the present case was neglected up to an advanced MG disease, the lower limbs edema being associated with inframesocolic space fluid collection, bilateral pleural effusion and right breast edema. Doppler DE proved a useful tool in detecting and characterizing of the unsuspected BC; the size of the tumor was overestimated by Mammography, due both to the tissular compression and tumor flattening during the examination, and to the problems of delimitating of the neoplastic mass from the surrounding spicules of the connective tissue. Moreover, the axillary lymph nodes characterization was concordant at DE and needle puncture-aspiration biopsy, but over diagnosed at mammography.

This case of secondary MG has a particular complex etiology, presenting both C Hepatitis with elevated viremia, and BC; moreover, the staging of the neoplasia is difficult to establish, because the size and extension of the lesion is falsely increased by the edematous disease. The stage T4b was assessed according to the TNM

classification for tumor of any size and edema (including “peau d’orange”) of the skin, which do not meet the criteria for inflammatory carcinoma (it would be stage T4d); there were no nipple retraction, no rapid development, no lymph nodes involvement, and no subdermal lymphatics or small nodules visible in US, features more suggesting for inflammatory breast cancer, which usually has not a salient clinical and radiological lump. In the case presented above, the breast inflammation seems to be secondary to edema; moreover, the lymphocytes are frequently found associated with breast cancer in other cases than carcinomatous mastitis. The absence of the axillary lymphadenopathy suggests a nephrogenic breast lymphedema, concordant with the right pleural effusion larger than the pleural effusion of the left side due to the preferential right lateral decubitus; however, the routine practice determined a clinical TNM classification with overestimation of T character and a delay in the surgical treatment.

3. CONCLUSIONS

There are few cases reported in the literature with paraneoplastic MG and BC, but many cases may be missed because of a wrong evaluation; the kidney biopsy is not routinely performed in known BC with nephrotic syndrome, usually the etiology of the edematous syndrome being attributed to other causes or considered idiopathic.

However, the etiological-pathological diagnosis is important, because the surgical and chemotherapeutical treatment of the BC can resolve the nephrotic syndrome, and inversely, the resolution of the proteinuria with hypoproteinemia might be a measure of the prognosis of the disease [6]. An important aspect of the reported cases with paraneoplastic MG was the advanced local stage of the breast malignancy, type invasive ductal cancer, but without any lymph nodes involvement [6].

The incidence of the paraneoplastic MG may be underestimated sometimes because of the metachronous association of the proteinuria and hypoproteinemia with advanced BC; in a report of Valcamonico et al. [10] the nephrotic syndrome appeared five years after the diagnosis of BC. Despite the absence of widely accepted experimental model of the association of glomerulopathy and cancer, the remission of the proteinuria after complete healing of the neoplasia represents a clinical proof of etiological correlation.

The deficiency of this case report is the missing of the therapeutic result, which would prove the relation cause-effect in paraneoplastic MG already demonstrated in literature; however, this rare case of MG associated with BC and C hepatitis illustrates the severity of the nephrotic syndrome, by one side, and the utility of the anatomical breast Ultrasonography, the DE, with its standardized technique of acquisition and interpreting, which can be performed in breast screening [11]. The specific finding of the anatomical 2D radial and antiradial scanning completed with the Doppler malignant characters of the new formation vasculature (multipolar with incident angle of the plunging artery) were sufficient in the detection and characterization of the breast malignancy, in this case the Mammography being used as complementary method of diagnosis due to the less 40 year-old patient and to the less accuracy in beast edema. In addition, a quick US evaluation detected the pleural effusions, the peritoneal fluid with specific location and the non-invasive Doppler examination allowed us to eliminate any venous thrombosis that would influence the lower limbs edema.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient for the use of its medical records in schooling and scientific aims, including publication of this paper and accompanying images; a patient consent form of our own institution was obtained during her hospitalization.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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