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immunocytochemistry and flow cytometry is critical in making the diagnosis.

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Observation of an association between ground-glass-like globules in Papanicolaou smears and bacterial vaginosis

Dear Editor,

Bacterial vaginosis (BV) is the most common vaginal infection among women of childbearing age. Although the aetiology and pathogenesis of BV remain a matter of some controversy, it appears that the normal protective vaginal lactobacilli are replaced by anaerobic microorganisms. BV can have serious implications, including adverse pregnancy outcomes, increased susceptibility to sexually transmitted infections and infertility.¹

The Papanicolaou method is commonly used for diagnosing BV, providing an alternative to Gram-staining of smears,² and is capable of detecting BV in the majority of infected women, both symptomatic and asymptomatic.³

For several years, we have occasionally observed the presence of intriguing structures similar to "ground-glass-like" globules in cervico-vaginal (CV) smears from patients with BV stained using the Papanicolaou (Pap) method, which, to our knowledge, have not previously been reported in CV smears.

Thus, the aims of this Correspondence were to provide examples of the appearance of these globules, describe the frequency with which the structures were observed in CV smears, explore their significance, and question whether these globules are related to clinical factors such as age, presence of symptoms, the utilisation of any contraceptive method, or pregnancy.

A retrospective analysis was undertaken of all conventional CV smears submitted to a cytology laboratory in Spain over a 2-year

period (2013–2014). All the smears had been stained using the Pap method. The percentage of specimens in which globules were observed under a light microscope was determined. A subset of nine positive smears for BV, which demonstrated the presence of globules, were chosen and re-stained with PAS, Masson's trichrome and Gram stain.

The clinical information for the patients' whose smears contained globules was reviewed to establish whether there was any correlation between the presence of globules in the Pap smears and BV. Four characteristics were taken into account: age, clinical symptoms, contraceptive use and pregnancy.

A total of 39 637 CV smears were submitted to the laboratory over a 2-year period. Of these, 18 slides were positive for the presence of these unusual globules (0.045%). The globules appeared as round structures (20–149 µm in diameter), with smooth and regular borders, a blue-greyish tonality, and with numerous coccobacilli adhering to their edges and covering their surfaces (Figure 1A, B).

A clear association was observed between the existence of globules and BV (18 cases; 1.15%). The difference between two proportions 0/38 123 vs 18/1514 is statistically significant at $P < .001$ (McNemar's test for difference between two proportions, Innersoft CAD v2.9; Middlesex University, London, UK).

The median age of patients with BV was 37.3 years (range 17–62). No statistical differences were found with regards to age and the presence of globules. Of the patients with BV, 877 (57.92%) had

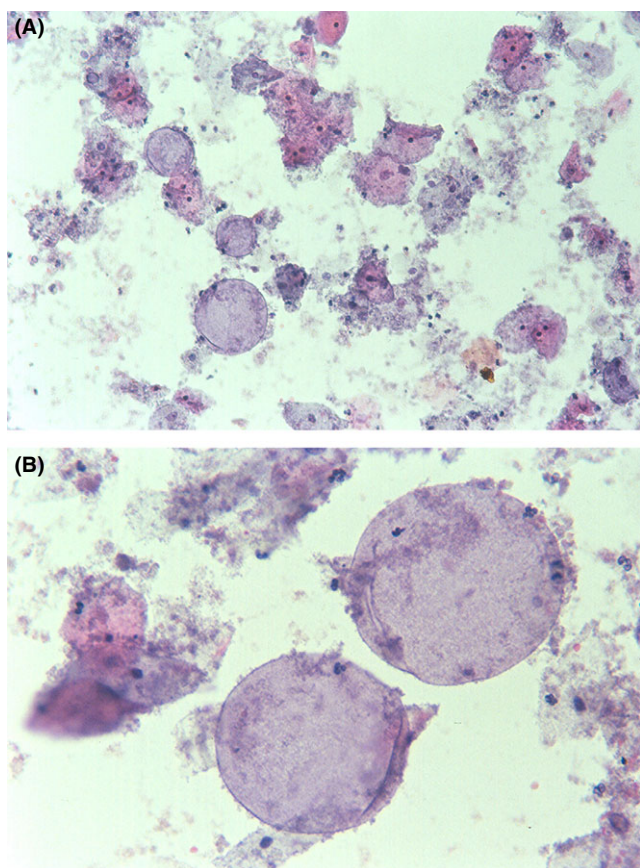


FIGURE 1 “Ground-glass-like globules” in a Pap smear. (A) among numerous “clue cells” we observed some round structures (Papanicolaou stain, $\times 200$). (B) a higher magnification of these round structures with smooth and regular borders, a blue-greyish tonality, and with numerous coccobacilli adhering to their edges and covering their surfaces (Papanicolaou, $\times 400$).

symptoms (the most frequent being vaginal discharge with malodour and vulvovaginal itching). In 17 of the 18 cases where globules were observed (94%), symptoms of BV were also reported; one case was asymptomatic.

When the presence of globules was compared against contraceptive use, 11 cases did not utilise any contraceptive methods, and seven cases did (spermicidal gel – three cases, oral hormonal contraceptives – three cases and IUD – one case).

Of the patients with BV, 47 (3.10%) were pregnant, but globules were not observed in any of the samples from pregnant women.

Neither PAS nor Masson's trichrome stained the globules. The Gram stain showed numerous “clue cells” in a background with abundant coccobacilli and leukocytes, but the globules did not stain well with this stain either.

As the results obtained by a range of stains (PAS, Masson's trichrome and Gram) were negative, the nature of these globules continues to be uncertain. It is possible to speculate that globules were

associated with more significant cases of infection. The chief complaint of patients with BV is malodorous (“fishy” odour) greyish white vaginal discharge. This malodour has been linked to increased vaginal biogenic amines such as the polyamines putrescine, cadaverine and trimethylamine. Alterations in the metabolism of amino acids (marked elevations of cadaverine and putrescine), carbohydrates (higher levels of succinate) and lipids (higher levels of 4-hydroxybutyrate and 13-hydroxyoctadecadienoic acid) have been demonstrated in BV.⁴ Thus, we hypothesize that the production of these amines, and the associated metabolic changes mentioned above, may be associated with the production of gas in the vaginal milieu (in BV the vaginal discharge has a frothy appearance) and may be related to the origin and existence of these globules in the Pap smears.

To the best of our knowledge, this is the first time that this type of structure has been reported in CV smears. Further studies are needed which assess the relationship between these “ground-glass-like” globules and BV in Pap smears, to clarify the origin and nature of these globules, and to assess whether they may be a marker of virulence, or are associated with some microorganism.

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