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Original article

Metabolic syndrome is not associated with greater evidences of proliferative inflammatory atrophy and inflammation in patients with suspected prostate cancer

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Abstract

Introduction and objectives: To evaluate the association between metabolic syndrome (MetS) and proliferative inflammatory atrophy (PIA) in patients with suspected prostate cancer (PCa).

Patients and methods: From June 2015 to July 2016, we conducted the FIERY (Flogosis Increased Events of pRostatic biopsY) study at the Urology section, Department of Surgery of the University of Catania (Local registration number: #131/2015).

A total of 205 patients with elevated prostate-specific antigen (≥ 4 ng/ml) or clinical suspicion of PCa who underwent primary transperineal prostate biopsy were included in this cross-sectional study.

The assessment of PIA, HGPIN, and PCa were performed by 2 experienced pathologists and samples were investigated for the presence of an inflammatory infiltrate, according to the Irani score. Primary and secondary Gleason grade of tumor in positive biopsies were evaluated according to the 2016 ISUP Modified Gleason System.

Results: In the entire cohort, median age was 68.0 (interquartile range: 62.0–74.5), median prostate-specific antigen was 6.5 (interquartile range: 5.51–9.57). The prevalence of MetS was 34.1%, the detection rate of PCa was 32.7%, the rate of PIA was 28.3%, the rate of HGPIN was 32.2%, whereas the rate of severe intraprostatic inflammation (Irani-score ≥4) was 28.8%.

When comparing clinical and histological variables in patients without and with PIA, metabolic aberrations where not significantly different in both groups. We did not find statistical association in detection rate of PCa (29.3% vs. 34.0%; $P = 0.07$) and HGPIN (27.6% vs. 34.0%; $P = 0.37$) in patients with and without PIA, respectively. When considering metabolic aberrations, MetS was not associated with Irani-score ≥4 (28.6% vs. 28.4%; $P = 0.96$) and none of each component was statistically predictive of severe inflammation.

At the multivariable logistic regression analysis, PIA, HGPIN, and MetS were not associated with greater risk of PCa.

Conclusion: In this study, we did not show an association between MetS and PIA and PCa. Although the small sample size and the cross-sectional nature of the study, we do not suppose that MetS could be associated with greater evidence of PIA. Further studies should be conducted to evaluate the exact nature of this pathological lesion.

Keywords: High-grade prostatic intraepithelial neoplasia; Metabolic syndrome; Proliferative inflammatory atrophy; Prostate cancer; Risk factors

1. Introduction

Prostate cancer (PCa) represents the most common incident cancer in men in developed countries in 2013 [1]. Recent epidemiological studies supported the evidences for a genetic predisposition for PCa, based on 2 of the most important factors, racial/ethnic background and family history [2]. Furthermore, some findings indicated that exogenous factors may be associated with the risk of transformation of a normal prostate cell into clinical PCa [3–5]. Among these factors, metabolic aberration, diet,

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alcohol consumption, and others have emerged owing to their potential implication in the pathogenesis of various cancers and gene expression, including PCa [6–9].

Recently we have demonstrated in a systematic review and meta-analysis that the presence of metabolic syndrome (MetS) was associated with worse oncologic outcomes in men with PCa, in particular with high-grade PCa and biochemical recurrence [10].

In fact, based also in the previous literature data, it is possible that MetS may activate several pathways including inflammation, insulin resistance, visceral adiposity, and hormone changes [11,12], and further increasing the risk of PCa and high-grade PCa.

Similarly, Cicione et al. [13] showed that PCa detection rate at repeat biopsy was significantly higher in patients with MetS and high-grade prostatic intraepithelial neoplasia (HGPIN) than in those with without MetS (57.4% vs. 23.5%; $P = 0.016$).

Although not routinely reported in the clinical practice, the proliferative inflammatory atrophy (PIA) may be present in the prostate biopsies in about 30% [14], and there are some evidences that supported the hypothesis of a morphologic transition between PIA, HGPIN, or adenocarcinoma or both [15].

These findings are supported by the evidences that PIA has some of the hallmark gene expression changes found in HGPIN and PCa. Moreover, a great deal of literature has addressed the role of genetic polymorphisms in inflammation pathways and the production of inflammatory cytokines with regard to PCa risk and promotion [16].

However, there are no data about the association of MetS with PIA and PCa.

In this study, we aimed to evaluate this relationship in a cohort of patients with prostate-specific antigen (PSA) ≥ 4 ng/ml and undergoing first prostate biopsy for suspected PCa.

2. Patients and Methods

From June 2015 to July 2016, we conducted the FIERY (Flogosis Increased Events of pRostatic biopsY) study at the Urology section, Department of Surgery of the University of Catania. The protocol was approved by the Internal Institutional Review Board and an informed written consent was obtained from each patient before the initiation of the study (Local registration number: #131/2015).

Two-hundred-five patients with elevated PSA (≥ 4 ng/ml) or positive digital rectal examination who underwent primary transperineal prostate biopsy were included in this cross-sectional study.

Men receiving 5 alpha reductase inhibitors, with bacterial prostatitis or previous prostate surgery before biopsy were excluded from the study. All prostate biopsies were performed under local anesthesia with at least 12 cores (median: 12; range: 12–24).

All surgical specimens were examined on hematoxylin and eosin-stained sections by 2 independent pathologists, blinded of any clinical information.

The assessment of PIA, HGPIN, and PCa were performed by 2 experienced pathologists R.C. and F.M. (Cohen's kappa coefficient = 0.81) and a discordance on the diagnosis was revised by a third expert pathologist which, after a careful discussion, has chosen the fairer one. PIA was described as focal simple atrophy (SA) or postatrophic hyperplasia (PAH) occurring in association with chronic inflammation, defined as focus of mononuclear inflammatory cells in the stroma, epithelium, or lumen accompanied or not by fibrosis. At low magnification, atrophy is characterized by architectural distortion and basophilic tinctorial quality caused by the reduction in cytoplasmic amount. Focal nucleolar prominence may sometimes be seen, mostly within the diffusely inflamed areas, but this is usually not as prominent as in the cancer cells. SA characteristics were: little amount of cytoplasm compared with normal epithelium; number of acini per unit area similar to normal epithelium; and acini of relatively normal caliber, albeit may be irregular or angulated. PAH consists of crowded small acini, mostly round and very close to each other, arranged in a lobular distribution. Often these acini seem to be surrounding a somewhat dilated "feeder" duct. The acini are lined by low cuboidal cells with very scant cytoplasm [17]. Pathologists examined the presence of PIA and HGPIN in all cores collected from the prostate biopsy.

Samples were investigated for the presence of an inflammatory infiltrate, according to the Irani score [18].

The resulting parameters were defined and scored as follows: Histologic grading (0 = no inflammatory cells, 1 = scattered inflammatory cell infiltrate without nodules, 2 = not confluent lymphoid nodules, and 3 = large inflammatory areas with confluence) and histologic aggressiveness (0 = no contact between inflammatory cells and glandular epithelium, 1 = contact between inflammation and epithelium, 2 = interstitial infiltrate with glandular disruption, and 3 = glandular disruption on >25%). The sum of this grading method ranged from 0 to 6. Grading did not include the types of inflammatory cells (polymorphonuclear leukocytes, lymphocytes, monocytes, or plasma cells).

Supplementary Figs. 1–3 show samples of SA, PAH, and inflammation in prostate biopsy.

Primary and secondary Gleason grade of tumor in positive biopsies were evaluated according to the 2016 ISUP Modified Gleason System [19].

Prior to prostate biopsy, each patient has been evaluated for the presence of MetS defined by the International Diabetes Federation (IDF). The IDF criteria defined MetS in the presence of 3 or more of the 5 characteristics of (1) waist circumference ≥94 cm; (2) triglycerides ≥150 mg/dl or treatment for hypertriglyceridemia; (3) high-density lipoprotein cholesterol < 40 mg/dl or treatment for reduced