

REVIEW ARTICLE

AZZOPARDI PHENOMENON

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ABSTRACT:

Azzopardi phenomenon is a histomorphologic phenomenon characterized by deposition of the basophilic material in the necrotic blood vessel walls associated with several malignant tumors. It was first correctly identified in 1959 by John G Azzopardi as DNA material associated with tumor necrosis. Azzopardi confirmed it to be DNA material that is liberated due to necrosis as it showed positive feulgen reaction. This process was considered to be seen in malignancies only, but various researches done in this field are unveiling the occurrence of Azzopardi phenomenon in other diseases apart from malignancies. Still now curtain is rising in this phenomenon as various new discoveries are being added up in it. This article aims to highlight reviews in the occurrence and presence of Azzopardi phenomenon.

Key words: Azzopardi phenomenon, blood vessels, DNA, Malignancies.

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INTRODUCTION

The Azzopardi effect is a histomorphologic phenomenon of incrustation of blood vessel wall with the basophilic nuclear material. It had been primarily described in small

cell (neuroendocrine) carcinoma of the lung but is nonspecific and can be seen in other malignancies with a rapid cell turnover.¹ Foci of strongly hematoxyphilic blood vessels appearing as the result of chromatin diffusion secondary to necrosis of neoplastic tissue are sometimes referred to as the Azzopardi phenomenon.²

This phenomenon was named after John G Azzopardi, who had identified the basophilic granular material in the vessel wall as DNA, after examining cases of small cell carcinoma of lungs.³

Prior to his publication, the material was infrequently described in the literature and was presumed to be caused by calcium deposition.⁴

It is associated with several malignancies such as small cell carcinoma, Burkits lymphoma, Merkel cell carcinoma and Medulloblastoma. Azzopardi performed histochemical analysis using van Kossa and Alizarin red staining methods and demonstrated a positive Feulgen reaction, suggesting that the basophilic material was DNA. He concluded that this phenomenon of DNA in the vessel wall is presumably

the result of deliberation of nucleic acids in large amounts from degenerating neoplastic cells.⁵

REVIEW

In the year 1959, John G Azzopardi examined 100 blocks of oat cell carcinoma, 32 cases showed peculiar bluish grey to the bluish black coloration of the walls of small venules. He also noted that there exists a striking association between necrosis in the tumor and the presence of this change. He correctly identified the basophilic material as DNA.⁶

Schmidt and coworkers in the year 1998, documented the presence of Azzopardi phenomenon in Merkel Cell Carcinoma.⁷ While as most recently Patterson and Wick, stated that Azzopardi phenomenon is never seen in primary endocrine tumors of skin, in particular, Merkel cell carcinoma.⁸ In 2007, Marina Vazmitel and Michal M reviewed 83 cases of Merkel cell Carcinoma. Azzopardi phenomenon was found only in 3 tumors.⁹ Azzopardi phenomenon has also been noted in diffuse large cell lymphoma.¹⁰

Shu Ling Peng et al. in 2007, reported the first case of Burkitt lymphoma associated with Azzopardi phenomenon.¹¹

Azzopardi also mentioned the association of tumor necrosis with this phenomenon. To clarify the relationship of Azzopardi effect with tumor necrosis in Burkitt lymphoma, they retrospectively reviewed 56 cases of Burkitt lymphoma in an archival file and evaluated the frequency and area of tumor necrosis. It was not found in any case. However, 28 cases showed tumor necrosis ranging from 5-7%. So, tumor necrosis is likely a sine qua but not a sufficient element for its formation. Other factors, such as pH, permeability, and solubility in the vessel wall endothelial cell function and tumor type may also play a vital role.¹¹

Hidehiro Takei et al. in 2007, investigated Azzopardi phenomenon in medulloblastoma/ primitive neuroectodermal tumors. Out of 102 cases that were retrieved from the anatomic pathology files of Texas Children Hospital, Azzopardi phenomenon was seen in 4 cases. They agreed with Azzopardi's conclusion that this phenomenon of DNA in the vessel wall is presumably the result of the liberation of nucleic acids in large amounts from degenerating neoplastic cells, given that this change was found to be confined to vessels adjacent to the large areas of tumor necrosis in all cases. However, tumor necrosis was shown in all the cases but not all showed Azzopardi phenomenon.¹²

Margarida Goncalves et al. in 2008, reported Azzopardi phenomenon in Lupic lymphadenitis. Peter Nau et al in 2010, reported two cases of small cell carcinoma of the gall bladder and noted Azzopardi phenomenon in both cases.¹³ Although Azzopardi phenomenon was primarily described in small cell carcinoma of lungs, Irache A.P et al. in 2016, reported the presence of Azzopardi phenomenon in Neuroendocrine small Cell Carcinoma of the Bladder.¹⁴

Josef Zustin et al in 2016, mentioned this phenomenon in cystic pseudotumors associated with retrieved metal on metal arthroplasty. Although Azzopardi phenomenon is seen in malignant tumors, they reported this phenomenon in periprosthetic tissue. They observed characteristic bluish substance in a pathologically changed periprosthetic membrane in four cases of adverse reactions to metal debris that clinically presented with progressive groin pain and radiographically characterized as so called pseudotumors. Several histochemical analyses were done and demonstrated positive Feulgen reaction.⁵

DISCUSSION

Foci of strongly hematoxyphilic blood vessels, appearing due to diffusion of DNA material is referred to as Azzopardi phenomenon, named after John G Azzopardi, who identified the basophilic material as DNA in 1959. He confirmed it by a positive Feulgen reaction and nuclear extraction methods. He also mentioned that DNA material present in the vessel wall is due to tumor necrosis. Earlier this peculiar vascular change was attributed to calcification by Oglivie and Mckeown. It was first noted in small cell carcinoma of lungs, afterward, it was documented in various other malignancies. In 2007, the first case of Burkitt

Lymphoma associated with Azzopardi phenomenon was reported.⁵⁻⁷

The cause behind Azzopardi phenomenon is believed to be tumor necrosis, but various studies showed tumor necrosis without Azzopardi effect. Tumor necrosis is most commonly associated with the release of DNA material, A study done by Shung Ling Peng found out that tumor necrosis was present in all the cases they were examining but none showed Azzopardi phenomenon, so it can be said that tumor necrosis may be an additional factor not the only factor for Azzopardi phenomenon. Other factors which could have played important role in Azzopardi phenomenon are pH, permeability, and solubility in the vessel wall. The presence of Azzopardi phenomenon in Merkel cell carcinoma was favored by some authors like Schmidt, while it was questioned by Patterson and Wick who clearly mentioned that Azzopardi phenomenon is never seen in Merkel cell carcinoma. To clear the confusion Marina V also examined 83 cases of Merkel cell carcinoma, and Azzopardi phenomenon was seen only in 3 cases. This phenomenon has been reported by various authors in neuroendocrine tumor of bladder, lupic lymphadenitis etc.⁸⁻¹¹

Although the Azzopardi phenomenon represented a specific morphological pattern which can be seen in several malignant tumors, the presence of this phenomenon in non-neoplastic conditions has also been reported. Josef Zustin et al. reported Azzopardi phenomenon in four patients in retrieved metal on metal arthroplasty unrelated to malignancy.⁵

CONCLUSION

Azzopardi phenomenon represents a rare phenomenon with the specific morphologic pattern which can be seen in several malignancies. Although tumor necrosis is considered to play vital role in its formation, other factors such as pH, a permeability of vessel wall etc should also be considered. Many histological, histochemical and ultrastructural studies have been conducted, since its discovery. Still, exact histogenesis and associated diseases have not been correctly elucidated. So, we can conclude that although it's a rare finding, pathologists should have knowledge regarding this histomorphologic appearance while examining soft tissue sections.

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