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Clinicopathological Characteristics of Pathogenic Germline Variant Carriers

Michael Emery*

Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

INTRODUICTION

Pathogenic Germline Variants (PGVs) are inherited genetic mutations present in all cells of the body, and they contribute significantly to the development of various cancers and inherited syndromes. Understanding the clinic pathological characteristics of PGV carriers is essential for improving cancer risk assessment, early detection, and personalized treatment. This article explores the clinic pathological features commonly observed in individuals with pathogenic germline variants, with a focus on how these characteristics differ from those of sporadic cases and influence clinical decision-making.

DESCRIPTION

Genetic basis of pathogenic germline variants

Pathogenic germline variants can be found in tumor suppressor genes, oncogenes, and DNA repair genes, and they are frequently associated with cancer syndromes. For example, mutations in tumor suppressor genes such as *BRCA1*, *BRCA2*, *TP53*, and *APC* are associated with hereditary breast, ovarian, and colorectal cancers. Similarly, variants in DNA mismatch repair (MMR) genes, such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, underlie Lynch syndrome, which predisposes individuals to colorectal, endometrial, and other cancers. Understanding the genetic basis helps clinicians assess cancer risk in PGV carriers, establish surveillance protocols, and choose targeted therapies.

Age of onset and cancer risk

One of the hallmark clinicopathological features of PGV carriers is an earlier-than-typical age of cancer onset. Individuals with PGVs often develop cancer at a younger age than those with sporadic forms of the disease. For instance, BRCA1 and BRCA2 mutation carriers have a significantly increased risk of breast and ovarian cancer, often diagnosed before the age of 50. Likewise, Lynch syndrome-associated colorectal cancer frequently arises before age 50, contrasting with the sporadic cases that typically present later. The early age of onset in PGV carriers emphasizes the importance of genetic testing for individuals with family histories of early-onset cancer, as this can guide timely surveillance and preventive strategies.

Furthermore, cancer risk among PGV carriers is markedly higher than in the general population. Studies have shown that carriers of *BRCA1* or *BRCA2* mutations have a lifetime breast cancer risk of up to 70%, compared to approximately 13% in the general population. Similarly, Lynch syndrome mutation carriers have a lifetime risk of colorectal cancer that can exceed 50%, compared to a 4-5% risk in the general population. These heightened risks underscore the importance of identifying PGV carriers to implement early detection measures and reduce cancer-related morbidity and mortality.

Tumor characteristics

The presence of a PGV is often associated with specific tumor characteristics, which can differ from those seen in sporadic cancers. In breast cancer, for example, *BRCA1* mutation carriers are more likely to develop Triple-Negative Breast Cancer (TNBC), which lacks estrogen, progesterone, and *HER2* receptors. This phenotype is clinically significant as TNBC is associated with a more aggressive course and limited treatment options. In contrast, *BRCA2* mutation-associated breast cancers are often hormone receptor-positive, affecting treatment selection and prognosis.

Multisystem involvement and synchronous tumors

Another important characteristic of PGV carriers is the potential for multisystem involvement and the occurrence of synchronous or metachronous tumors. In syndromes such as Li-Fraumeni syndrome, which is caused by pathogenic variants in TP53, carriers are at risk for a broad spectrum of cancers, including breast, bone, brain, and adrenal gland cancers. These individuals may develop multiple primary tumors over their lifetime, necessitating comprehensive surveillance protocols covering multiple organ systems.

Correspondence to: Michael Emery, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; E-mail: michael.esd@gmail.com

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Implications for treatment and management

The presence of a PGV influences treatment decisions, as certain targeted therapies are more effective in these patients. For example, *BRCA1* and *BRCA2* mutation carriers may benefit from poly (ADP-ribose) polymerase (PARP) inhibitors, which exploit the defect in DNA repair mechanisms to induce cell death. Clinical trials have shown that PARP inhibitors can significantly improve progression-free survival in *BRCA*-mutated ovarian and breast cancers, establishing them as a key treatment option in these patients.

Furthermore, MSI-high colorectal cancers in Lynch syndrome patients have shown better responses to immune checkpoint inhibitors such as pembrolizumab. In 2020, the FDA approved pembrolizumab for MSI-high or MMR-deficient solid tumors, highlighting the importance of MSI testing in PGV carriers for whom immunotherapy may be a valuable treatment option.

Prophylactic surgeries are also considered for high-risk PGV carriers, particularly for those with *BRCA1*, *BRCA2*, or *APC* mutations. For example, risk-reducing mastectomy and oophorectomy are options for *BRCA* mutation carriers to decrease the risk of breast and ovarian cancers. Similarly, prophylactic colectomy may be indicated in individuals with Familial Adenomatous Polyposis (FAP), which is caused by APC mutations, to prevent colorectal cancer.

Psychosocial and familial implications

Carrying a PGV has psychosocial and familial implications that extend beyond clinical features. Knowing one's genetic predisposition can cause anxiety, stress, and feelings of uncertainty, particularly for individuals with a high lifetime cancer risk or a history of multiple family members with cancer. Genetic counseling is essential for helping PGV carriers understand their risks, make informed decisions about surveillance and preventive measures, and manage the emotional impact of their genetic status.

For family members, the identification of a PGV may have significant implications. Predictive genetic testing can determine if relatives also carry the variant and are at increased risk. This information enables tailored surveillance for family members, potentially reducing cancer incidence and mortality within families. Furthermore, family members may consider options such as prophylactic surgery or other preventive measures if they are found to carry the pathogenic variant.

CONCLUSION

Clinicopathological characteristics of pathogenic germline variant carriers reveal significant distinctions from sporadic cases, including earlier age of onset, unique tumor features, multisystem involvement, and increased cancer risk. These characteristics have profound implications for cancer risk assessment, screening, and management, underscoring the importance of genetic testing and counseling in clinical practice. Understanding the clinicopathological traits of PGV carriers allows for a proactive, personalized approach to cancer care, benefiting both patients and their families by improving outcomes and enabling informed decision-making.