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Research Article

Genetic Mutational Status and Tumour-inflammatory Response in Metastatic Cancer: New Implications for Exploring Immunotherapies

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Abstract

While genetic mutations can offer targeted therapy for some cancer patients, many patients have tumours that lack currently utilised genetic treatment targets. With the advent of immune-modulator cancer therapy, we evaluated the relationship between genetic mutation status and tumour-associated inflammatory response in 56 needle biopsies of tumour metastases. From histopathology clinical audit data, we documented the range of metastatic tumour types in adult female and male patients and noted their histologic and molecular characteristics. Surrounding inflammatory response to these tumours was graded according to severity. Presence of genetic mutations used in targeted treatment was associated with weak inflammation while absence of these mutations was associated with brisk inflammation. As targeted therapy is not available for patients with tumours lacking specific genetic mutations, it is worth exploring whether they may benefit from immune-based treatments.

Keywords: Cancer Immunotherapy; Tumour-inflammatory Response; Genetic Mutation; Targeted Therapy; Immune Modulation

Introduction

Metastatic cancer poses some of the greatest challenges in modern oncology and cancer management [1]. While metastatic tumours with specific genetic mutations can be treated with targeted therapy [1,2], no such treatment exists for those without these mutations, and they are typically treated with systemically toxic chemotherapy agents [3]. We documented genetic mutation status and tumour-associated inflammatory response in tumour metastases to assess the relationship between these two variables considering that immune-based treatments may be worthy of study in treating tumours without genetic-based treatment targets. We reviewed anonymised histopathology clinical audit data regarding the histology, molecular findings and tumour-associated inflammation of metastatic tumours from 56 needle biopsies of male and female patients, aged 42 to 90 years. Histology and molecular data were gleaned from anonymized archived histopathology reports. Inflammation grading was performed on H&E slide review for each case. Twice as many tumours without genetic mutations had brisk inflammatory response compared to tumours with genetic mutations. Similarly, twice as many tumours with genetic mutations had a weak inflammatory response compared to tumours without mutations.

Methods

Anonymised histopathology data from clinical audit of 56 needle biopsies of metastatic lesions were reviewed (as documented in Royal College of Physicians Faculty of Pathology Continuing Professional Development Scheme). Results from molecular studies for EGFR, KRAS, BRAF, N-RAS, and ROS-1 genetic mutations and ALK rearrangements were compared with degree of inflammatory response surrounding metastatic tumour. Inflammation grading was performed by consultant histopathologist (PHH) by light

microscopic review of H&E biopsy slides as having either 'brisk' or 'weak' inflammatory response. Genetic mutation analysis was performed at molecular laboratory, Beaumont Hospital, Royal College of Surgeons in Ireland.

Results and Discussion

Of 56 metastatic tumours, all were adenocarcinomas from primary sites including 22 colorectal, 12 pancreatic, 7 lung, 7 breast, 4 upper gastro-intestinal, 3 gallbladder, and 1 prostate. When reported, tumors were poorly (15), moderately (29) and well (1) differentiated. Of 24 cases tested, 13 tumours had genetic mutations identified including EGFR, KRAS, N-RAS, and BRAF. Tumour-associated inflammation was 'brisk' or 'weak' (Figure 1 a and b). Twice as many tumours without genetic mutations (6) had brisk inflammatory response compared to tumours with genetic mutations (3). Similarly, twice as many tumours with genetic mutations (10) had a weak inflammatory response compared to tumours without mutations (5; Figure 2). No other clinical or pathologic variables revealed an association with genetic mutation status or degree of inflammation.

Figure 1a: Brisk inflammatory response surrounding tumour.

Figure 1b: Weak inflammatory response surrounding tumour.

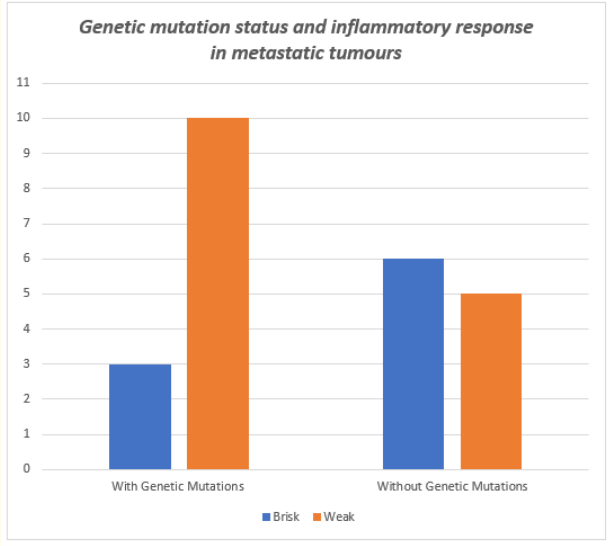

Figure 2: Genetic mutation status and inflammatory response in metastatic tumours.

Metastases defines stage IV disease in most cancers and is often treatment refractory to conventional chemotherapies [3]. Primary and metastatic tumours can be tested for the presence of one of several genetic mutations for which targeted therapy is available, often with good response [4-7]. Patients with tumours, particularly those with metastases, often have limited, if any, remaining treatment options aside from palliative care. We evaluated the association between targetable genetic mutation status and tumour-associated inflammatory response to help support the potential utility of further exploring immune-based therapies in patients whose tumours lack targeted therapy options.

A deciding factor in the efficacy of treatments for metastatic cancer is the immune microenvironment and its dynamic interplay with neoplastic cells [8-10]. An important role of the immune system is to both identify and eliminate tumours. Tumour-associated antigens not found on healthy cells are recognized as "non-self" and an immune response is thereby mounted against the tumour cells. Biological response modifiers, such as interferons and interleukins, may be used to bolster the immune system by introducing larger amounts of these substances by injection or infusion with the hope of stimulating the cells of the immune system to act more effectively [11,12]. Tumour survival is promoted with upregulation by tumour cells of inflammatory inhibitors protective against tumour-associated inflammation. In lung, colorectal and

head and neck cancers, immunotherapy blocking inflammatory inhibitors, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death-1 (PD-1) pathway, has been used to elicit immune-mediated destruction of tumour cells with promising results [11,12]. In ovarian cancer, tumour-infiltrating lymphocytes have been demonstrated to be associated with better prognosis, more chemosensitivity, and more cases of optimal residual tumour, and may be a potent predictive immunotherapy biomarker [13]. In colon cancer, tumour-infiltrating lymphocytes and lymphoid reactions have been associated with favourable prognosis [14,15], while KRAS mutations, similar to mutations in our study, have been shown to be associated with cases that did not possess such a tumour-inflammatory response [16].

Conclusion

In our data review, we found that twice as many tumours without genetic mutations had brisk inflammatory response compared to tumours with genetic mutations. It was particularly interesting to note the reverse relationship that twice as many tumours with genetic mutations had a weak inflammatory response compared to tumours without mutations. Although larger samples are needed, there may be a clinically useful association between genetic mutation status and inflammatory response in that approaches that bolster tumour-reactive inflammatory response may prove useful in patients that have exhausted or been found refractory to other treatment options. We propose further exploration into the utility of immunotherapies that enhance the efficacy of tumour-associated inflammation, particularly in patients with tumours lacking genetic therapeutic targets.

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Conflict of Interest

Authors have nothing to disclose.

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