CLINICAL VIGNETTE

CHEK2 Variant in a Patient with Multi-Malignancies

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Case Presentation

An 82-year-old male presented with multiple lung nodules. He had multiple prior resections of primary basal cell carcinoma (BCC) over 15 years. These nodules were in the arms, calf, shoulder and upper abdomen included: metastatic squamous cell carcinoma in the chest since 2004; resected melanoma in situ in the mid back in 2014 and resected malignant melanoma in the right lower leg in 2019. (See Figure 1a for histopathology.) Surveillance PET-CT noted lung nodules with focal intense FDG uptake in the right middle lobe and left lower lobe (LLL) (see Figure 2a and 2b). Past medical history includes chronic hypotension; heart failure; CAD; dyslipidemia; paroxysmmal atrial flutter; type 2 diabetes and benign prostatic hyperplasia.

LLL lung biopsy demonstrated metastatic malignant melanoma positive for S-100, HMB45 and Melan-A immunohistochemistry stains (see Figure 1b). RML biopsy was forgone as it was assumed the same metastatic melanoma. He was started on pembrolizumab and underwent stereotactic body radiation therapy (SBRT) to the left lower lobe.

Two years later he was found to have IgM monoclonal gammopathy with abnormally high light chain ratio and underwent bone marrow biopsy. Pathology indicated 30-50% cellular bone marrow with paratrabecular nodular infiltrates of small- to intermediate-sized lymphocytes, staining positive for CD20, BCL2, PAX5, consistent with small B-cell lymphoma (see Figure 3). The patient was monitored with serial serum protein electrophoresis. No additional chemotherapy was started given stable IgM levels, and a lack of systemic symptoms on pembrolizumab.

One year surveillance PET-CT demonstrated sclerotic lesions in the right iliac bone, right femoral neck, and T11 and L1 vertebral bodies with increased FDG uptake (see Figure 4). Right iliac bone biopsy was consistent with metastatic prostatic adenocarcinoma, staining positive for AE1/AE3, PSAP, PSA. The patient was started on androgen deprivation therapy (ADT) regimen of leuprolide and apalutamide. After 10 months of ADT and 7-8 months of apalutamide, PSA decreased from 42 to 0.2, however prostate specific membrane antigen (PSMA) PET scan did not show meaningful response to therapy. Worsening pain and lack of significant therapeutic response raised concern for small cell transformation of the prostate adenocarcinoma. Repeat biopsy of the iliac bone lesion revealed identical histology. The patient's pain gradually subsided and repeat PSMA scans showed some degree of response. He is currently on cycle 30 of pembrolizumab and dose 4 of leuprolide. Eighteen months ago he underwent germline genetic testing of 117 genes associated with hereditary cancers. The only finding was a heterozygous *CHEK2* variant of uncertain significance, c.7C>T. Given persistently elevated troponin he was evaluated for possible immune-mediated myocarditis. Serial imaging and labs indicated no significant change in cardiac function from prior to immunotherapy. Pembrolizumab was held after two years of treatment given the concern for myocarditis.

Discussion

Malignant melanoma, prostate cancer, and small B-cell lymphoma are distinct neoplasms, with unique etiologies, risk factors, and management. Melanoma, the most aggressive form of skin cancer, arises from the uncontrolled proliferation of melanocytes, often due to ultraviolet radiation exposure. Prostate cancer is the second most common cancer in men worldwide, originating from the prostate gland and often associated with advancing age, family history, and genetic factors. Small B-cell lymphoma encompasses a heterogeneous group of lymphoid neoplasms characterized by the clonal expansion of small, mature-appearing B cells. These malignancies have diverse clinical presentations and outcomes, depending on the specific subtype and stage at diagnosis. Our 82-year-old male with chronic hypotension, heart failure, and melanoma subsequently developed recurrent melanoma with metastases to the lungs, IgM lambda monoclonal gammopathy, small B-cell

lymphoma, and prostate cancer with metastases to the axial skeleton.

This patient presented with rapid onset of multiple malignancies. Recurrence of melanoma is not uncommon. However, development of small B-cell lymphoma and metastatic prostate cancer within a year is rare.

A *CHEK2* variant of uncertain significance was the only notable finding in a comprehensive multigene germline panel. *CHEK2* pathogenic/likely pathogenic variants have traditionally been associated with autosomal dominant susceptibility to breast, prostate, colorectal, and other cancers including gastric, kidney, osteosarcoma and thyroid.[1-3] The patient's specific mutation, c.7C>T, is predicted to result in the amino acid substitution p.Arg3Trp. Evidence supporting pathogenicity includes report of the variant in several patients with breast cancer, one with B cell lymphoma, and another with prostate cancer.[4-6] The literature on the cellular consequences of this variant reports this variant is unlikely to significantly impact protein function but may slightly impair DNA damage response.[7] Though the variant may be the underlying cause for this patient's multiple cancers, his age, absence of cancer in relatives and the variant's uncertain significance did not support additional screening such as, colonoscopy in this patient and family members.

His status as a Veteran is a risk factor that may have increased likelihood of developing malignancies. Non-Hodgkin lymphoma and prostate cancer are listed as having an associated with Agent Orange exposure. Although he served in Vietnam, he did not have documented exposure to Agent Orange, or report exposure. Veterans frequently have histories of smoking and alcohol use. This patient had no smoking history and minimal use of alcohol.

Chemotherapy of multiple malignancies involved extensive collaboration between oncology, dermatology, primary care, and medical genetics. When he was initially diagnosed with small B-cell lymphoma with secondary Waldenstrom's macroglobulinemia, he was already undergoing chemotherapy with pembrolizumab for his melanoma. A decision was made to not introduce a second systemic chemotherapy, because pembrolizumab provides some coverage for lymphoma. Although SBRT for metastatic melanoma is not approved as standard of care, ongoing trials and retrospective studies showed potential benefit with some abscopal effect to the non-radiated lesion. Pembrolizumab was chosen to treat the melanoma instead of ipilimumab/nivolumab given the patient's relatively low disease burden and multiple comorbidities. While bone marrow biopsy is not routinely used to evaluate low risk MGUS, this patient's exceptionally high light chain ratio warranted biopsy. Androgen deprivation therapy was initially deferred while evaluating for cardiac amyloidosis that was negative. Androgen deprivation therapy was initiated for prostate malignancy. The expected lifespan for patients with metastatic melanoma is at least two to three years. This patient has remained relatively asymptomatic for the past three years without evidence of disease progression.

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Figures

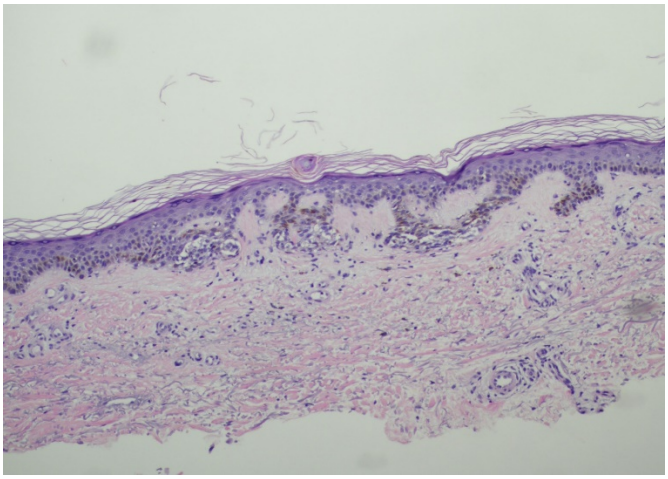

Figure 1a: The melanocytic lesion displays melanocyte overgrowth and bridging at the dermal-epidermal junction. This melanoma *in situ* is does not show signs of vertical growth.

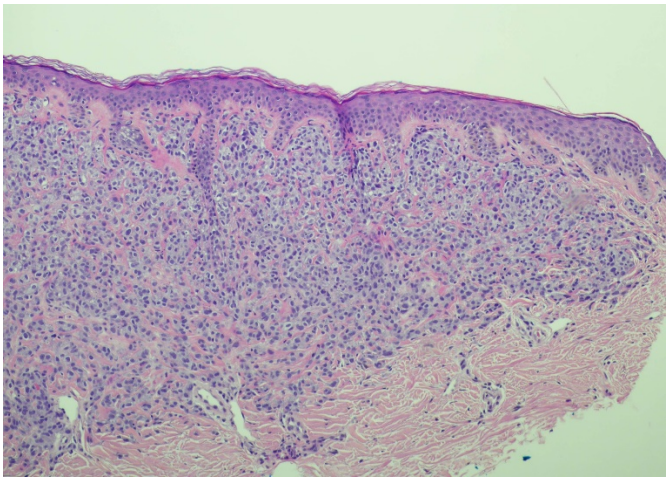

Figure 1b: The second melanocytic lesion demonstrates an extension of the melanoma into the dermis, with melanocyte overgrowth but without bridging. This nodular melanoma extends into the reticular dermis.

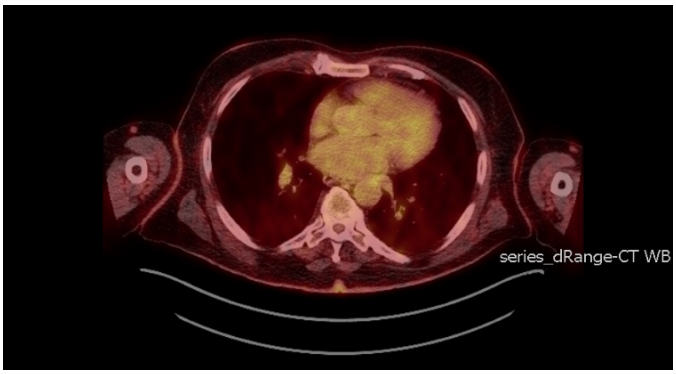

Figure 2a: Right middle lobe hypermetabolic lung nodules with focal intense FDG uptake on PET-CT completed in January 2021.

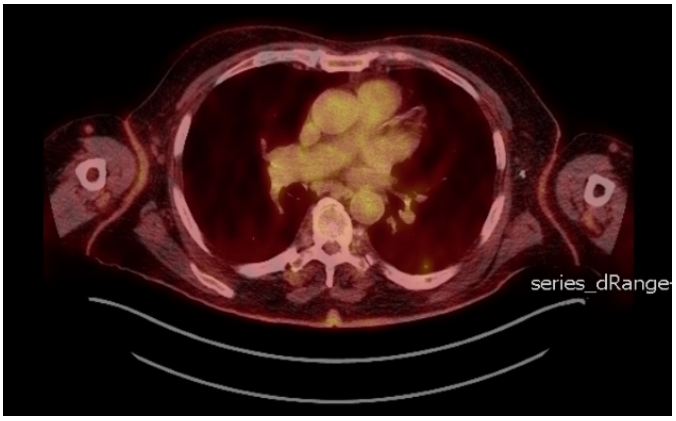

Figure 2b: Left lower lobe hypermetabolic lung nodules with focal intense FDG uptake on PET-CT completed in January 2021.

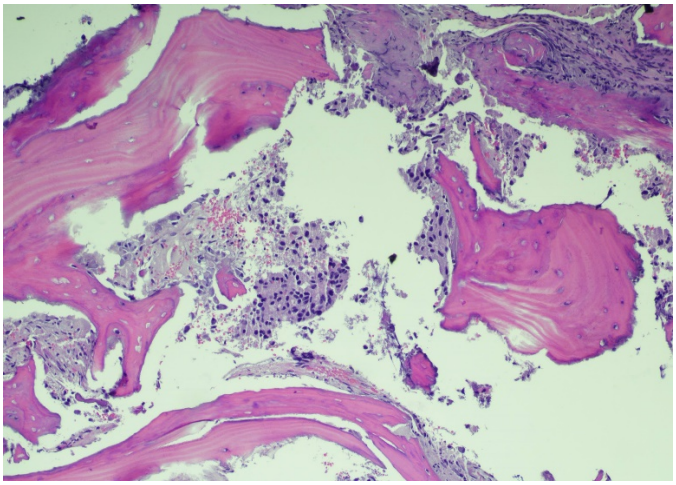
Figure 3: The bone marrow biopsy reveals bone marrow elements and spicules of bone with clustered epithelial cells indicating metastatic carcinoma within the bone marrow.

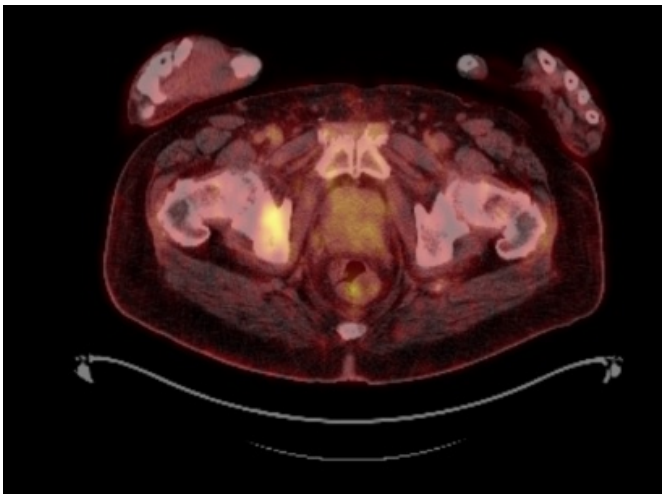
Figure 4: Sclerotic lesions with increased FDG uptake in the right iliac bone on PET-CT completed in January 2022.

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