Cells to Surgery Quiz: June 2021

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WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of Rajiv I. Nijhawan, Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Cells to Surgery Quiz. In this monthly online-only quiz, the first question (“What is your diagnosis?”) relates to the clinical image shown, while additional questions concern the findings reported in the JID article by Poizeau et al. (2021) (https://doi.org/10.1016/j.jid.2020.07.038).

Detailed answers and a list of relevant references are available following the Quiz Questions below.

QUIZ QUESTIONS

1. What is your diagnosis of the marked lesion on the left lower calf?
   a. Actinic keratosis
   b. Bowen’s disease
   c. Malignant melanoma
   d. Basal cell carcinoma
   e. Dermatofibroma

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Cells to Surgery Quiz

2. Which of the following statements is true regarding the overall survival in patients with metastatic melanoma?
   a. Treatment of metastatic melanoma with a combination of nivolumab and ipilimumab leads to a decreased overall survival compared with treatment with ipilimumab alone.
   b. Female sex has been associated with a survival disadvantage in patients treated for melanoma of the head and neck.
   c. Lower socioeconomic status is associated with decreased melanoma incidence and increased overall survival.
   d. Patients who receive anti–PD-1 antibodies (also referred to as PD-1 inhibitors) as first-line treatment for metastatic melanoma have a higher overall 2-year survival rate than patients who receive ipilimumab or cytotoxic chemotherapy.
   e. *BRAF*-mutant melanoma is associated with a significant survival disadvantage when compared with non-*BRAF*-mutant melanoma.

3. Which of the following is false regarding the real-world approach to studying melanoma survival rates taken by Poizeau et al. (2021)
   a. Patients being treated with targeted therapies for *BRAF*-mutant melanoma demonstrated increasingly improved overall survival across the cohorts for whom targeted therapies were available.
   b. The lungs were found to be the most common distant site of melanoma metastasis.
   c. Study data indicate that patients with melanoma are now being treated earlier in the disease course.
   d. Survival curves show a more rapid effect for patients treated with targeted therapies than for those treated with immune checkpoint inhibitors (ICIs) but longer remission for those treated with ICIs and/or worse prognosis in *BRAF*-mutant melanoma.
   e. Real-world patients with melanoma receiving a given treatment had lower overall survival than patients receiving that same treatment in a randomized control trial.

See following pages for detailed answers.
DETAILED ANSWERS

1. What is your diagnosis of the marked lesion on the left lower calf?

CORRECT ANSWER: **c. Malignant melanoma.**

Malignant melanoma classically presents as an asymmetric, variegated macule or papule with an irregular border and variable diameter (Kibbi et al., 2016). Given the clinical appearance of this lesion, a biopsy was performed, and it confirmed superficially spreading malignant melanoma with a Breslow depth of 0.4 mm. Of note, on examination, the patient also had extensive background damage and numerous nevi all over his body. The patient has tested negative for CDKN1a mutations implicated in BRAF-mutant melanoma (Jalili et al., 2012). Given his extensive skin cancer history at an incredibly young age, he was referred for further genetic testing, which he declined.

Approximately 30% of superficially spreading melanomas have been found to arise from existing nevi (Pampena et al., 2017). Histologically, superficially spreading melanoma demonstrates a period of radial growth in the epidermis followed by invasion into the dermis (Clark et al., 1969). Melanoma incidence has been increasing over the past several decades; the most important environmental risk factor is exposure to UV rays (Rastrelli et al., 2014). Meanwhile, the number of total body nevi is one of the strongest risk factors for melanoma development, with the risk for melanoma development increasing linearly with the number of total body nevi (Bhatt et al., 2016). Patients with dysplastic nevi are also at increased risk for melanoma development (Arumi-Uria et al., 2003). However, as opposed to the linear increase in melanoma risk seen with typical nevi, melanoma risk does not continue to increase above five dysplastic nevi (Garbe et al., 1994).

Hereditary melanoma often appears as familial atypical multiple mole melanoma (FAMMM) syndrome, characterized by over 50 dysplastic nevi and a positive family history of melanoma; these patients are at drastically increased risk for melanoma development (Soura et al., 2016). Mutations at the CDKN2a locus are most often implicated in FAMMM syndrome, and these patients are also at increased risk for pancreatic cancer (Soura et al., 2016). In addition, xeroderma pigmentosum is an autosomal recessive disorder in nucleotide excision repair genes, which confers more than a 2,000-fold risk for the development of melanoma (Black, 2016).

**Discussion of incorrect answers:**

- **a. Actinic keratoses:** Actinic keratoses (AK) are considered precancerous and precursor lesions to squamous cell carcinomas (SCCs). Clinically, AKs present as rough, erythematous papules or plaques with scale (Moy, 2000), and whereas AKs can be pigmented (James et al., 1978), this lesion appears to be more of a melanocytic lesion clinically. A biopsy is necessary for histologic confirmation. AKs are the third most common reason that patients see dermatologists, after dermatitis and acne (Reinehr and Bakos, 2019), and UVR exposure is the most significant risk factor for the development of AKs (Siegel et al., 2017).

- **b. Bowen's disease:** Bowen's disease, also known as SCC in situ, are lesions characterized histologically by full-thickness epidermal dysplasia; they become SCC once they breach the dermis (Mohandas et al., 2020). Clinically, Bowen's disease presents as well-demarcated hyperkeratotic papules or plaques (Lee and Wick, 1990). Similar to AKs, Bowen's disease can appear pigmented, but the lesion in Figure 1 is more suspicious for a melanocytic neoplasm. Pigmented SCCs are rare, with a reported frequency of 0.01–7% of total SCCs (Satter, 2007).

- **d. Basal cell carcinoma:** Basal cell carcinoma (BCC) is the most common malignancy in the United States, with the incidence increasing annually (Kim et al., 2019). Mutations in the Shh pathway, most commonly in the Hedgehog pathway gene PTCH1, drive the pathogenesis of BCC (Bonilla et al., 2016). BCCs usually present as pink, pearly papules (Kim et al., 2019). Histology of BCC demonstrates basaloid cells with peripheral palisading and clefting between the epithelium and the stroma (Maloney, 1995). Pigmented BCC is less common (Iain et al., 2012), but a biopsy is necessary to confirm the diagnosis.

- **e. Dermatofibromas:** Dermatofibromas (DFs) present as firm papules or nodules, most commonly on the extremities (Myers and Fillman, 2021). These lesions have an unclear etiology (Myers and Fillman, 2021). Patients may report trauma to the site where the DF presents, which points toward a reactive process; however, this theory has been challenged, with some arguing that the lesion represents a neoplastic process (Hui et al., 2002). The cutaneous entity in Figure 1 is less likely to be a DF because DFs often have a white stellate–like scar centrally (Agero et al., 2006).

2. Which of the following statements is true regarding the overall survival in patients with metastatic melanoma?

CORRECT ANSWER: **d. Patients who receive anti–PD-1 antibodies (also referred to as PD-1 inhibitors) as first-line**
treatment for metastatic melanoma have a higher overall 2-year survival rate than patients receiving ipilimumab or cytotoxic chemotherapy.

Melanoma is the deadliest type of skin cancer (Miller and Mihm, 2006). Recently, mAbs that inhibit immune checkpoints have become the preferred frontline therapy for metastatic melanoma (Wilson and Schuchter, 2016). Ipilimumab, a mAb against CTLA-4, was approved in 2011 and increased the overall survival rates in metastatic melanoma (Rendon and Rayi, 2021). CTLA-4 is an inhibitory receptor that downregulates T-cell activation when bound to B7 proteins on antigen-presenting cells (Jacob, 2015). In melanoma, cancer cells release ligands that bind to CTLA-4 and therefore decrease the T-cell response to the tumor (Bhandaru and Rotte, 2019). By preventing the activation of the CTLA-4 signaling cascade, ipilimumab increases T-cell activity against cancer cells.

Meanwhile, PD-1 is an inhibitory receptor that downregulates T-cell activation when bound to PD-L1 or PD-L2 ligands on tumor cells (Jacob, 2015). mAbs against PD-1 such as nivolumab prevent this interaction between cancer cells and T cells, increasing the immune system’s activity against the tumor (Rendon and Rayi, 2021).

Poizeau et al. (2021) examined the overall survival in all French patients treated for cutaneous metastatic melanoma between 2010 and 2017. They found that 48.4% of patients who received an anti–PD-1 antibody as a first-line treatment survived to 24 months. However, only 42.2% of patients who received ipilimumab and 23.8% of patients who received cytotoxic chemotherapy survived to 24 months (Poizeau et al., 2021).

Discussion of incorrect answers:

a. Treatment of metastatic melanoma with a combination of nivolumab and ipilimumab leads to a decreased overall survival compared with treatment with ipilimumab alone: In a randomized control trial, Hodi et al. (2016) found that patients treated for advanced melanoma with a combination of nivolumab (an anti–PD-1 antibody) and ipilimumab (an anti–CTLA-4 antibody) had a 2-year survival rate of 63.8%, whereas patients treated with ipilimumab alone had a 2-year survival rate of 53.6%. However, grade 3 or 4 adverse events (AEs) occurred in 54% of patients treated with combination therapy and 20% of patients treated with single-agent ipilimumab (Hodi et al., 2016). The increased AE profile of combination therapy has been described in further studies with minimal increases in overall survival and should be taken into consideration when choosing a first-line therapy (Wolchok et al., 2017).

b. Female sex has been associated with a survival disadvantage in patients treated for melanoma of the head and neck: Hanson et al. (2020) retrospectively reviewed 50,397 cases of head and neck melanoma and found that male sex conferred a significant survival disadvantage.

c. Lower socioeconomic status is associated with decreased melanoma incidence and increased overall survival: Studies analyzing the relationship between socioeconomic status and melanoma outcomes have indicated that low socioeconomic status is associated with increased melanoma incidence and decreased overall survival (Idorn and Wulf, 2014; Singh et al., 2011).

d. BRAF-mutant melanoma is associated with a significant survival disadvantage when compared with non–BRAF-mutant melanoma: Conflicting studies have emerged regarding the prognostic effect of BRAF-mutant melanoma. For example, Shinozaki et al. (2007) found that BRAF-mutant melanoma was associated with a significantly decreased median overall survival, whereas Urugel et al. (2007) concluded that the BRAF mutation does not stand as an independent prognostic factor. Additional research is necessary to better characterize the impact of BRAF mutation status on the prognosis of patients with melanoma.

d. A significant number of patients receiving ipilimumab for metastatic melanoma have experienced severe adverse effects.

e. Real-world patients with melanoma receiving a given treatment had lower overall survival rates than patients receiving that same treatment in a randomized control trial.

Poizeau et al. (2021) examined the outcomes of every patient treated systemically for cutaneous metastatic melanoma in France from 2010 to 2017. This observational study design is contrasted with randomized control trials, in which patients are excluded on the basis of characteristics such as severe comorbidities or brain metastases (Poizeau et al., 2021). Moreover, chemotherapeutic treatments in clinical trials have been shown to be less toxic and therefore potentially more effective than they are in the real world (Fraser et al., 2011; Prasad et al., 2014). The authors postulate that because of these two factors, overall survival is expected to be higher in randomized control trials than in the real world. So, one purpose of the study by Poizeau et al. (2021) was to examine the extent to which successful clinical trials have translated to improved real-world survival for patients with melanoma.
Contrary to expectations, Poizeau et al. (2021) found that not all treatments had higher survival rates in clinical trials than in the real world. Patients who received ipilimumab as a first-line treatment in the real world had a higher 24-month overall survival of 36% than the 29% overall survival of those who received ipilimumab in clinical trials (Ugurel et al., 2017). The authors attribute this difference to the availability of anti–PD-1 antibodies to real-world patients as a second-line therapy, which were not available to patients in ipilimumab’s clinical trials (Poizeau et al., 2021).

Discussion of incorrect answers:

a. Patients being treated with targeted therapies for BRAF-mutant melanoma demonstrated increasingly improved overall survival across the cohorts for whom targeted therapies were available: In BRAF-mutant melanoma, a substitution of V with glutamic acid (most commonly) in the BRAF oncogene results in unchecked cellular proliferation and therefore cancer (Sun et al., 2020). Therapies targeted at BRAF-mutant melanoma include BRAF inhibitors, which exhibit antitumor properties by blocking the action of the BRAF protein, and MAPK/extracellular signal–regulated kinase (MEK) inhibitors, which do the same by inhibiting MEK, a downstream protein in the BRAF signaling cascade (Sun et al., 2020). In the study by Poizeau et al. (2021), targeted therapies provided increasing median overall survival rates across the cohorts for whom targeted therapies were available. The authors attribute this increased survival to both the availability of novel second-line therapies in the later cohorts and the improved efficacy of combined BRAF and MEK inhibitor therapy versus that of BRAF inhibitor monotherapy (Flaherty et al., 2012). The data presented by Poizeau et al. (2021) support previous findings that there is a more rapid effect with targeted therapy than longer remissions with immune checkpoint inhibitors (ICIs).

b. The lungs were found to be the most common distant site of melanoma metastasis: In melanoma, metastasis to distant sites impacts a significantly worse prognosis than nonmetastatic melanoma (Balch et al., 2001). The lungs have been shown to be one of the most common sites of distant metastasis in melanoma (Damsky et al., 2010). Accordingly, Poizeau et al. (2021) found that the lungs were the most common site of distant metastasis in each cohort.

c. Study data indicate that patients with melanoma are now being treated earlier in the disease course: Supplementary Table S3 in the study by Poizeau et al. (2021) shows how patients who might not have received treatment before the advent of new melanoma therapies, such as asymptomatic patients with metastatic disease, are now treated earlier in their disease course.

d. Survival curves show a more rapid effect for patients treated with targeted therapies than for those treated with immune checkpoint inhibitors (ICIs) but longer remission for those treated with ICIs and/or worse prognosis in BRAF-mutant melanoma: Figure 4 in the study by Poizeau et al. (2021) compares the overall survival for patients in each cohort who received ICIs (anti–CTLA-4 antibodies or anti–PD-1 antibodies) for wild-type melanoma with the overall survival for patients in that same cohort who received treatment with targeted therapies for BRAF-mutant melanoma (Poizeau et al., 2021). Patients who received targeted therapies for BRAF-mutant melanoma had higher overall survival rates over the first 8 months, whereas patients who received ICIs for wild-type melanoma were more likely to survive to 24 months. This indicates that targeted therapies take effect more quickly than immune checkpoint inhibitors but that ICIs are more likely to lead to a longer remission and/or that BRAF-mutant melanoma has an intrinsically worse prognosis (Poizeau et al., 2021).

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