

Kaplan USMLE Step 1: Young boy gets blistering sunburn

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If you're preparing for the United States Medical Licensing Examination[®] (USMLE[®]) Step 1 exam, you might want to know which questions are most often missed by test-prep takers. Check out this example from Kaplan Medical, and read an expert explanation of the answer. Also check out all posts in this series.

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This month's stumper

A 2-year-old boy is brought in by his mother to the physician because she is concerned by how easily he gets sunburned. She states that he cannot be outside for barely five minutes without getting a painful, blistering sunburn. Physical examination shows a well-developed child with dry skin, many freckles, multiple actinic keratoses on the dorsum of his hands, and bloodshot eyes. Neither of the child's parents has ever had similar symptoms.

This child's condition is most likely caused by a defect in which of the following cellular processes?

- A. Base excision repair.
- B. Homologous recombination.
- C. Mismatch repair.
- D. Non-homologous end joining.
- E. Nucleotide excision repair.

The correct answer is E.

Kaplan Medical explains why

This child's history of severe sunburns with only minimal UV exposure combined with physical exam findings of freckling, xeroderma, actinic keratoses, and bloodshot eyes are all indications that the boy has xeroderma pigmentosum (XP). Patients with XP have an extremely high risk of developing skin cancer (as many as 50% will develop skin cancer by age 10) and blindness (often due to cataracts or corneal ulcerations).

The condition is caused by a defect in one of several enzymes involved in nucleotide excision repair. When DNA is exposed to UV radiation, thymine dimers form between adjacent thymine bases in a DNA strand. Normally, these thymine dimers are recognized, removed, and replaced. However, in the absence of normal XP repair proteins, the dimers remain, increasing the risk of causing mutations during DNA replication and thereby leading to the development of skin cancer. There are multiple genes that can be mutated in XP, but it is not important to learn these groups. Most forms of the disease are autosomal recessive, although some cases do arise *de novo*.

Treatment involves avoiding further exposure to damaging UV radiation and removing precancerous keratoses to prevent progression. Even with adequate precautions, life expectancy is poor.

Why the other answers are wrong

Choice A: Defects in base excision repair are seen in many cancers. In base excision repair, glycosylases (e.g., DNA glycosylase) remove damaged bases, thus creating an apurinic/apyrimidinic (AP) site. An AP endonuclease removes the deoxyribose 5'-phosphate and the resulting gaps in bases are filled by DNA polymerase and re-sealed by ligase. This most commonly occurs during G1.

Choice B: Defects in homologous recombination are seen in many conditions including Bloom syndrome, Fanconi anemia, and breast cancer due to *BRCA1* and *BRCA2* mutations. During late S phase or G2 phase, homologous recombination is the process by which sister chromatids are used as templates to repair double-strand DNA breaks. Because the opposite strand is used as a template, this process can also lead to a loss of heterozygosity.

Choice C: Defects in mismatch repair are seen in hereditary nonpolyposis colorectal cancer (Lynch syndrome). This process is used to repair abnormal A/C or G/T base pairs in the DNA. First, the newly synthesized DNA strand is differentiated from the parent strand. Then, mismatched pairs are recognized, spliced open, removed, repaired, and resealed. Lynch syndrome is caused by inheriting one absent copy of either *MLH1* or *MSH2*. The second copy is then lost through somatic mutation during the patient's life. The absence of both copies of this enzyme leads to microsatellite instability, which is diagnostic of Lynch syndrome and leads to an increased risk of colorectal cancer.

Choice D: Defects in non-homologous end joining are seen in severe combined immunodeficiency.

This process functions to repair breaks in double-stranded DNA caused by free radicals or ionizing radiation. Unlike homologous recombination that uses sister chromatids as a template for repairs, non-homologous end joining occurs prior to S phase when no sister chromatids are available. DNA ligase IV is involved in this process.

Tips to remember

- | Xeroderma pigmentosum is an autosomal recessive condition caused by defects in nucleotide excision repair.
- | Children present clinically with severe sunburn following minimal UV exposure and signs of skin damage (freckling, actinic keratoses, hyperpigmentation, eye lesions).
- | Treatment is the avoidance of further UV exposure, but the prognosis is poor, with most patients developing skin cancer during their lifetime.

For more prep questions on USMLE Steps 1, 2 and 3, view other posts in this series.