Lesson 317: Preanesthetic Assessment of the Patient With Xeroderma Pigmentosum

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
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Professional Gaps

Xeroderma pigmentosum, while uncommon, is a pathologic condition in which many of the usual approaches to anesthesia and analgesia are contrain-dicated or require a higher level of monitoring. Although most anesthesiologists may be aware of the condition, an appreciation of the pathogenesis and management is required to ensure the safest perioperative outcome.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. Define xeroderma pigmentosum
2. Describe the special circumstances associated with the administration of anesthesia to affected patients
3. List the clinical manifestations of xeroderma pigmentosum
4. Explain the present understanding of the pathophysiology of xeroderma pigmentosum
5. Determine appropriate preoperative care
6. Interpret the results of relevant genetic testing
7. Formulate a plan for anesthetic and analgesic administration
8. Review primary preventive measures for care of patients with xeroderma pigmentosum
9. State the incidence and prevalence of xeroderma pigmentosum
10. Predict, recognize, and respond to common perioperative complications
Case

A 14-year-old, 35-kg white girl presented with a history of numerous pigmented lesions over her face and extremities that progressively increased in size and number. Diagnostic pathology revealed well-differentiated basal cell carcinoma in several large lesions around her right supraorbital area and nose. Wide excision and skin grafting were planned. The clustered lesions around the nose suggested possible difficulty with mask ventilation, but airway assessment was normal. The anesthesia team noted a high level of anxiety in the patient and her family, and questioned further to ensure completeness of information. Her parents reported that the patient experienced an adverse reaction to anesthesia related to a prolonged effect of muscle relaxation after a previous surgery, after which she spent 1 day in the ICU requiring assisted ventilation. Past records from an outside hospital revealed that the patient received both midazolam and vecuronium during the general anesthetic, while undergoing another skin grafting 2 years previously.

Incidence

Xeroderma pigmentosum (XP), a type of genodermatosis, is an extremely rare, genetic, autosomal recessive disease, and is believed to currently affect 200,000 people in the United States. Males and females are equally affected, as are all races; European and North American populations have a frequency of 1 in 250,000 to 1,000,000, with the incidence increasing to 1 in 50,000 in North Africa and 1 in 30,000 among the Japanese—most likely due to high consanguinity. As detailed further, patients with XP have a high predisposition for the development of skin cancers, with the average age of onset of 8 years, which is roughly 5 to 6 decades earlier than average. Almost all patients develop some form of carcinoma or malignant melanoma before 20 years of age. Such statistics suggest that the frequency of skin cancer among those afflicted with XP is between 2,000- and 10,000-fold more than is found in the general population.

Pathophysiology

In addition to regulating body temperature and providing sensory feedback, the skin acts as a natural barrier to the environment, protecting the human body from conditions such as fluid loss, microorganism infestations, and ultraviolet (UV) radiation exposure. In patients with XP, several genes—which normally encode proteins responsible for repairing errors in DNA—are genetically mutated and inherited in an autosomal recessive manner. Such a mutation leaves the skin of XP patients vulnerable to UV-induced DNA damage. Normal, unaffected adults repair DNA damage incurred from sun exposure through 3 mechanisms: nucleotide excision repair, base excision repair, and DNA mismatch repair.

Of these mechanisms, nucleotide excision repair is defective in XP patients, resulting in the inability to remove so-called “thymine dimers.” These dimers are formed when UV light causes a free radical chain reaction across adjacent carbon atoms of pyrimidine nucleotides found within the DNA double helix—essentially creating a kink in the DNA. These dimers can be thought of as mistakes within the genome, and if not removed by repair proteins, provide a nidus for future replication errors because of their ability to distort the normal DNA architecture.

Eight genes have been identified as being mutated in XP. Seven of these genes (XPA, XPB, XPC, XPD, XPE, XPF, and XPG) are responsible for translating proteins needed for nucleotide excision repair, and are heterogeneously mutated in XP. The eighth gene, XPV, is involved in producing a protein used in error-
free semiconservative replication.\textsuperscript{3,4} The \textit{XPC} and \textit{XPE} genes yield proteins capable of identifying whether damage from UV radiation has occurred to the DNA, and the \textit{XPA} protein product acts as an authenticator, ensuring that an error (such as a thymine dimer) actually exists. After verification, the DNA double helix is unwound by XPB in a 3’ to 5’ fashion, and XPD unwinds from 5’ to 3’, culminating in XPF and XPG cutting the DNA adjacent to the error site.

If any one component of this process is disrupted, the thymine dimers will not be removed, and cell division will continue uncontrollably or fail altogether. Generally, this uncontrolled, error-inclusive replication is the basis for cancer formation. XP patients manifest their specific defect in DNA repair through extreme photosensitivity, sunlight-induced cancers, and neurodegeneration simply because DNA damage to the skin is so easily caused by UV exposure.

The most common defects in XP occur in the \textit{XPA} and \textit{XPC} genes. According to Kramer and Slor, \textit{XPA} mutations give rise to the greatest defect in protein translation, with virtually no chance of DNA repair.\textsuperscript{5,6} Patients with XP have differing complementations (which can be thought of as permutations) of these genotypes, leading to varying ability to repair DNA damage. However, regardless of the genetic combinations, most XP patients have overlapping clinical phenotypes. The slow accumulation of thymine dimers within the genetic structure results in the dysregulation of cell division. Inconsistencies in cell division over a relatively long period of time lead to multiple cutaneous, ocular and eventually neurologic consequences.\textsuperscript{7,8}

\textbf{Clinical Manifestations}

Individuals with XP may have normal-appearing skin at birth, but the skin eventually becomes dry, scaly, and hyperpigmented as sun exposure increases. Extreme photophobia and conjunctivitis are common initial complaints, and patients endure photosensitivity near the eyes and any areas of exposed skin. Manifestations of XP almost always appear before the age of 2 years (with the majority of children diagnosed in early infancy), and become obvious to caregivers due to the overwhelming sunburn children suffer in only minutes of outdoor exposure.\textsuperscript{1,5}

Dermatologists are usually the first clinicians to make the diagnosis based on this extreme sun sensitivity. Confirmation is accomplished through a unique cellular test that provides a visualization of any defect in the nucleotide excision repair process.\textsuperscript{2} Although some affected children may only experience moderate reddening of the skin, almost all affected with the \textit{XPC} defect suffer serious burns leading to long-lasting blisters.

Individuals with XP all have freckling of the face, arms, and lips in addition to the hallmark features of xeroderma (dry, itchy, scaly skin) and poikiloderma (variation in skin pigmentation with widened capillaries). Freckles tend to be irregularly shaped and range from small and pinpoint to over a centimeter in size. Excessive freckling is thought to be a result of melanocyte mutagenesis. Eventually, XP patients develop malignant melanomas, keratoacanthomas, angiomas, fibromas, and sarcomas that can number from one to more than 180.\textsuperscript{1,5}

Ocular manifestations emerge in approximately 40\% of XP patients, presenting commonly as blepharospasm and photophobia. Other symptoms include eyelid atrophy, tumors, corneal sicca and opacification, exposure keratitis, pterygium, telangiectasias, loss of lashes, chronic conjunctival injection, and malignancy. Unlike XP’s closely related counterpart, Cockayne syndrome (another defective nucleotide excision–repair disease), retinal abnormalities are rare. The most commonly reported cancers
affect the eyelids, conjunctiva, limbus, cornea, and iris, and encompass squamous and basal cell carcinomas, keratoacanthomas, melanomas, and leiomyosarcomas. Current guidelines suggest Mohs’ micrographic surgery is best for the complete resection of eyelid tumors, reserving cryotherapy and irradiation for conjunctival malignancies.1,3,5

Neurologic deficiencies are some of the most common abnormalities of XP, and are found in up to 20% to 30% of patients with the XPA, XPD, and XPG genotypes. However, a recent longitudinal study examining the neurologic status of XPC patients discovered no deficits over a 15-year period in this subtype. Nonetheless, as a consequence of immature brain development, neuronal loss in the cerebrum and cerebellum, and axonal degeneration in the periphery, many XP individuals may be born with short stature and microcephaly, only to experience progressive mental deterioration, intellectual impairment, emotional lability, ataxia, spasticity, sensorineural deafness, hyporeflexia or areflexia, peripheral neuropathy, and choreoathetosis with increasing age.9

To clarify, genetic derangements, rather than congenital physical abnormalities—for example, microcephaly—are the source of the progressive decline in cognitive status. Anttinen et al identified the order in which these abnormalities emerge, beginning slowly at the age of 2, becoming more evident nearing ages 4 to 5, and almost all appearing by the age of 8.1,10 The typical neurologic features of the different subtypes of XP by the gene affected are shown in the Table.

<table>
<thead>
<tr>
<th>Complementation Group</th>
<th>Gene</th>
<th>Cutaneous Neoplasia</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>XPA</td>
<td>+</td>
<td>XP with mild to severe neurologic abnormalities</td>
</tr>
<tr>
<td>B1</td>
<td>ERCC3</td>
<td>+</td>
<td>XP/CS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−</td>
<td>TTD</td>
</tr>
<tr>
<td>C</td>
<td>XPC</td>
<td>+</td>
<td>XP with mild neurologic abnormalities</td>
</tr>
<tr>
<td>D4</td>
<td>ERCC2</td>
<td>+</td>
<td>XP with no neurologic abnormalities to severe neurologic abnormalities</td>
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<tr>
<td></td>
<td></td>
<td>+</td>
<td>XP/CS</td>
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<td></td>
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<td>−</td>
<td>COFS syndrome</td>
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<tr>
<td>E</td>
<td>DDB2</td>
<td>+ 5</td>
<td>XP with no neurologic abnormalities</td>
</tr>
<tr>
<td>F</td>
<td>ERCC4</td>
<td>+</td>
<td>XP with no neurologic abnormalities or severe late-onset neurologic abnormalities; Fanconi anemia (FA) complementation group Q; one individual with features of XP, CS, and FA, and 2 individuals with CS</td>
</tr>
<tr>
<td>G</td>
<td>ERCC5</td>
<td>+</td>
<td>XP with no neurologic abnormalities or severe neurologic abnormalities</td>
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<tr>
<td></td>
<td></td>
<td>+</td>
<td>XP/CS</td>
</tr>
<tr>
<td>Variant 10</td>
<td>POLH</td>
<td>+</td>
<td>XP with no neurologic abnormalities</td>
</tr>
</tbody>
</table>

*+, present; −, absent; 5, cerebrooculoskeletal; TTD, trichothiodystrophy (without XP); XP/CS, xeroderma pigmentosum–Cockayne syndrome complex; XP/TTD, trichothiodystrophy with XP
Involvement of the perioral area and oropharynx, although clinically rare, is very important when considering intubation. An anecdotal case outlined several hazardous features in a 29-year-old XP patient with poor dental hygiene that affected the oral mucosa.11 Widely spaced maxillary teeth with marked anterior projection showed evidence of calculus deposits and enamel hypoplasia.

Periodontal disease resulted in red, inflamed, and recessed gingiva. A single sessile squamous cell carcinoma was noted on the tip of the tongue. Blistering throughout the buccal mucosa had led to scarring and greatly reduced the ability to open the mouth.

**Treatment and Indications for Surgery**

There is no cure for XP, and the primary aim of current treatment modalities involves prevention of new skin cancer formation by strict sun avoidance. Interventions for avoiding unnecessary sun exposure include wearing protective clothing and sunscreen. All visible tumors should be removed frequently, with autologous unexposed skin grafts.2

A rather novel approach has been introduced by Yarosh et al, who applied topical T4 endonuclease V in liposomes to XP patients to repair sun-damaged skin.12 Kramer et al provide convincing evidence for supplementation with high-dose oral isotretinoin following tumor removal to mitigate future risk for regrowth.1,5,13 Recent advances in genetic therapy have shown promise in creating exogenous skin grafts grown ex vivo. Dupuy et al strategize that cells taken from the epidermis could be genetically modified with viruses containing the wild-type gene, rendering them UV-resistant.2 Imiquimod 5% cream—an immune system modifier—has been shown to eradicate refractory multiple basal cell carcinomas when applied for 4 months.14

**Anesthetic Considerations**

Several considerations factor into the anesthesiologist’s approach to an XP patient. First and foremost, the practitioner must exercise great care in handling the psychosocial impact any procedure may have on the patient and his or her family. Repeated exposure to surgery and anesthesia, coupled with the patient’s inherent susceptibility to physical insult, renders XP patients and their families exquisitely sensitive to the physical manipulation and isolation necessary for any procedure involving anesthesia. As mentioned above, many forms of XP feature significant neurocognitive abnormality, and while these neurocognitive features compound the psychosocial considerations, there are also physiologic concerns relevant to anesthesia, particularly in that XP patients have been shown to be hypersensitive to the synergistic effects of benzodiazepines and opioids.15 To avoid potential adverse reactions to opioids, analgesia is typically accomplished via supplementation with a nonsteroidal anti-inflammatory agent such as ketorolac, with minimal opioid use for breakthrough pain.15

Due to a propensity for dermatologic and joint injury in XP patients, the preoperative management of XP patients necessitates protection and padding of pressure points, and movement should be performed as gently as possible. The patient should be shielded from artificial light; this often means covering the entire patient to prevent exposure.16 Similar precautions must be maintained with regard to the patient’s eyes.

Along with the neurologic concerns, many patients with XP experience progressive neuromuscular derangements, which may manifest as stiffness of the mouth and neck. This clearly creates concern not only for airway management, but also renders patients overly susceptible to significant prolongation of
the effects of muscle relaxants. For this reason, minimal use of muscle relaxants is recommended, and if used, neuromuscular blockade must be carefully monitored. Several studies also recommend the avoidance of prolonged use of nitrous oxide, as it has been noted to cause myelosuppression to which XP patients are significantly vulnerable. Furthermore, Reitz and Lanz reported in an in vitro study halothane-induced DNA strand breaks in the lymphocytes of XP patients, with no such effect in the DNA of healthy human donors, suggesting a possible genotoxic effect of this inhalational agent in patients with DNA repair deficiencies.

Choice of anesthetic thus becomes difficult, although case reports have documented safe total IV techniques with propofol using spontaneous ventilation and laryngeal mask airway insertion; if a volatile agent is administered, it appears that sevoflurane is the preferred agent. It should be noted that an in vivo study has shown that both sevoflurane and isoflurane induce transitory DNA damage in human lymphocytes.

Therefore, best-practice strategies for XP patients would include spontaneous ventilation with either propofol as part of a total IV anesthesia technique or sevoflurane, as this has been shown clinically to be safe and effective. Additionally, nonsteroidal anti-inflammatory agents are safe and encouraged; opioids and benzodiazepines are potentially problematic and should be avoided.

An extensive review of world literature found that sevoflurane has been used without complication in several patients with XP, although Fjiouji et al reported a sole incident of neurologic deterioration in an XP patient anesthetized with sevoflurane. In that case report, a patient with XP developed considerable neurologic deficits only after surgical fixation of a femoral neck fracture performed under sevoflurane, although this complication may reflect fat emboli. Propofol exhibits many characteristics similar to sevoflurane, but is associated with the potential for an adiposity-dependent apneic effect, rendering it less than optimal in complicated and potentially sensitive XP patients who may be already at risk for airway compromise. Careful titration and reduced dosage are required. Total IV anesthesia (TIVA) using propofol in patients with good airways, however, has been described successfully and is generally recommended in the absence of airway compromise.

Dexmedetomidine has been suggested as an alternative to both medications, as it has sedative, analgesic, and anxiolytic effects with minimal respiratory depression. Presently, data on its use are limited, owing to concern about several potential adverse events, including hypotension, bradycardia, and nausea. Since these effects are dose-dependent, if dexmedetomidine is used, a best-practice strategy could include a reduced dosage for XP patients.

Management of the Case Presented

On the morning of surgery, 30 minutes prior to the establishment of venous access with a 22-gauge cannula, EMLA cream (lidocaine 2.5% and prilocaine 2.5%) in an emulsion was administered. The patient was not premedicated with benzodiazepines and the preoperative preparation room was kept dark. Ketorolac 30 mg was administered by IV for analgesia prior to induction of anesthesia. After preoxygenation with 100% oxygen, induction was facilitated with propofol 100 mg. Spontaneous ventilation was maintained. Classic laryngeal mask airway number 3 was inserted, and maintenance of anesthesia was accomplished with a propofol infusion at 50 to 75 mcg/kg per minute. Preemptive analgesia included administration of 0.5% ropivacaine to the surgical site. Spontaneous ventilation was maintained throughout the 118-minute surgery. The total estimated blood loss was less than 100 mL and a total of 1,900 mL of lactated Ringer’s solution was administered. Postsurgically, the patient recovered
from anesthesia without any issues. Ketorolac 30 mg was administered to supplement postoperative analgesia. The patient was discharged home on the first postoperative day.

**Conclusion**

A significant risk for adverse events, including the potential for a difficult airway and the likelihood of multiple perioperative drug sensitivities, means that the clinical anesthesiologist caring for a patient with the relatively rare disease XP must be especially methodical and vigilant. Potential problems include sensitivity to, and adverse effects from, certain anesthetic drugs. As such, the anesthesiologist must develop a safe perioperative anesthetic plan, restricting the administration of many commonly used drugs. The clinical anesthesiologist must plan for a possible failure to intubate as well as postanesthesia complications and positioning problems that can result in neurologic deficits. The proper choice of anesthetic drugs and technique are both vital to a successful procedure.

Owing to the rarity of the disease, a scarcity of information exists. Nevertheless, it is generally recommended to avoid volatile agents, which have been implicated in animal models as having genotoxic effects on XP patients. Instead, the selection of TIVA with propofol most likely should be the anesthetic technique of choice. Benzodiazepines and opioids also must be used with caution or avoided altogether because of their increased effects in patients with XP. Muscle relaxants should be kept to a minimum dose and carefully monitored because of their increased duration of action in XP patients.

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REFERENCES


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Post-test

1. Xeroderma pigmentosum is a disease characterized by what genetic deficiency?
   a. Base excision repair
   b. Nucleotide excision repair
   c. DNA mismatch repair
   d. RNA mismatch repair

2. Xeroderma pigmentosum is inherited in what kind of genetic fashion?
   a. Autosomal dominant
   b. X-linked
   c. Autosomal recessive
   d. Co-dominant

3. All of the following XP complementations are implicated in neurologic deficits except:
   a. XPA
   b. XPG
   c. XPC
   d. XPD

4. What is the average age at which XP patients are diagnosed with skin cancer?
   a. 2 years
   b. 8 years
   c. 20 years
   d. 50 years

5. What kind of dimer (the DNA defect responsible for Xeroderma pigmentosum) is formed in the DNA architecture of XP patients when they are exposed to UV radiation?
   a. Thymine-thymine
   b. Guanosine-guanosine
   c. Cytosine-cytosine
   d. Adenosine-adenosine
6. Precautions that should be taken into consideration prior to inducing the patient for anesthesia include:
   a. padding of pressure points
   b. shielding patient’s eyes from artificial light
   c. gentle handling of the patient when moving
   d. all of the above should be taken into consideration

7. Which drug should be avoided in XP patients, due to concerns about myelosuppression, when considering anesthesia?
   a. Succinylcholine
   b. Midazolam
   c. Nitrous oxide
   d. Sevoflurane

8. Which medication may be a safe alternative to propofol and sevoflurane, but still presents with dose-dependent side effects such as hypotension, bradycardia, and nausea?
   a. Dexmedetomidine
   b. Medetomidine
   c. Clonidine
   d. Phenothiazine

9. Why should halothane be avoided in XP patients?
   a. It may cause the formation of thymine-thymine dimers.
   b. It may induce DNA strand breaks in lymphocytes.
   c. It may enhance DNA replication.
   d. None of the above

10. Benzodiazepines and opioids should be used with caution, or entirely avoided, in XP patients because:
    a. they tend to have antagonistic effects
    b. they need higher doses to work effectively
    c. XP patients may be much more sensitive to them resulting in the potential for morbidity or mortality
    d. XP patients are susceptible to addiction