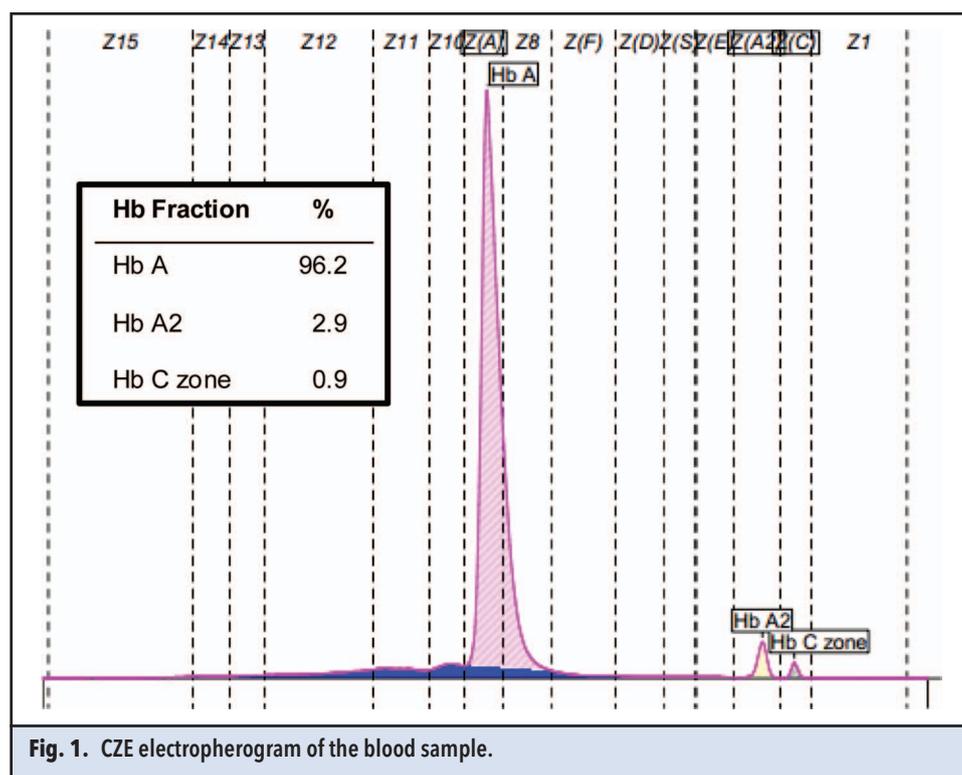


Hemoglobinopathy or Analytical Interference?

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CASE DESCRIPTION

A 59-year-old man was admitted for the investigation of mild chronic anemia (hemoglobin 11.0 g/dL). Hemoglobinopathy screening by capillary zone electrophoresis (CZE) was performed using the Capillarys Hemoglobin(e) kit (Sebia). An additional fraction in the Z(C) migration zone was observed on the electropherogram (Fig. 1).



QUESTIONS

1. What hypotheses can be put forward to explain the additional fraction observed in the Z(C) migration zone?
2. What approach should be adopted?

The answers are below.

ANSWERS

The additional fraction observed in the Z(C) migration zone can be due to the presence of either a Hb Constant

Spring variant (Hb A2: c.427T > C) or plasma proteins. Analytical interference in the form of plasma proteins is observed in anemic patients with decreased red blood

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cell:plasma ratios. As recommended by the manufacturer, CZE was performed on the red blood cell pellet from the same sample. The additional fraction was no longer observed, confirming plasma protein interference.

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News & Views

Differentiating Germline vs Somatic Variants in Cancer Tissue: Are Large-Panel Genetic Tests Helping or Hurting the Cancer Patient?

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The increased use of next-generation sequencing (NGS)² and increased understanding of tumor genetics have led to the identification of safer and more effective anticancer therapies. Unfortunately, solid tumors are genetically diverse, limiting the efficacy of targeted therapies to subsets of patients having specific genomic profiles. As a result, comprehensive genetic testing using NGS gene panels is becoming more common to help clinicians select appropriate therapies. A recent article in *Science Translational Medicine* (1) suggests that testing only tumor DNA and not germline DNA may lead to inappropriate administration of cancer therapies, resulting in patient safety concerns and increased healthcare costs. This study assessed 815 tumor-normal paired samples using either exome sequencing or a targeted 111-gene panel from patients with 15 different tumor types. By testing only tumors, they found false-positive results (i.e., misinterpretation of germline alterations as somatic) in 31% of alterations using the 111-gene panel and 65% of alterations by exome testing. They also found that 3% of patients with suspected somatic changes harbored germline alterations in cancer-predisposing genes. The authors concluded

that matched tumor-normal sequencing analyses are essential for precise identification and interpretation of genetic alterations for appropriate treatment of patients.

The majority of solid-tumor testing guidelines currently recommend individual gene or small gene panels to help clinicians determine whether specific drugs will have efficacy for a specific tumor type. These smaller gene assays, including “hotspot” or “targeted” NGS panels, assess important regions of the genome that should be well known to laboratories performing tumor-only tests. Clinical laboratories are less likely to misinterpret results from these panels because most detected variants are common and have known associations with specific therapies. Less commonly detected alterations with insufficient evidence to call pathogenic should be reported as variants of unknown significance (VUS). Testing laboratories and clinicians should not try to stretch VUSs into actionable mutations, because evidence-based therapies are driven by well-characterized mutations. Laboratories also need to state in their reports that NGS tumor-only assays cannot differentiate somatic vs germline variants and further testing may be necessary if a patient’s clinicopathologic and/or family history is suggestive of a hereditary cancer syndrome. Therefore, for smaller gene panel testing, running a second matched normal-tumor test for all patients may add cost to the healthcare system without significantly improving testing accuracy. In addition, germline variant interpretation is not without difficulty, and overinterpretation of germline alterations can potentially harm patients.

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² NGS, next-generation sequencing; VUS, variants of unknown significance.