Hyaluronic Acid is a Biomarker for Hemangiosarcoma Development

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Introduction

Hepatic hemangiosarcoma (HH) is a rare sinusoidal cell cancer linked to high level vinyl chloride (VC) exposure. This association was first recorded in 1974 in VC workers from Louisville, KY. To date, 26 out of 103 heavily exposed VC workers have developed HH, and routine liver chemistries were normal at diagnosis. Thus, diagnosis often occurs when the tumor is advanced. HH has a long latency period, (>30 years) and a poor prognosis (survival < 2 years). Biomarkers are needed for the early detection of HH. Potential serologic biomarkers for HH were measured in samples from VC workers. Healthy volunteers were used as controls. Hyaluronic acid (HA), cytokeratin-18 (CK-18), VEGF, IL-1β, IL-6, IL-8, IL-18, Leptin, TNF-α, MCP-1, PAI-1, TAS, and Adiponectin levels were measured. Hyaluronic acid, IL-8, IL-6, and cytokeratin-18 M65 fragment levels were elevated at the time of diagnosis of HH compared to healthy controls. No differences were seen for the other potential biomarkers. Elevated IL-8, IL-6, and CK-18 M65 are biomarkers for toxicant associated steatohepatitis. However, in workers developing HH, HA increased and crossed the reference range (0-54 ng/ml) from between 10-20 years prior to and progressively increased until diagnosis. Thus, a diagnosis of elevated HA could initiate a more rigorous monitoring program involving imaging which would allow earlier and more effective intervention for at-risk individuals.

Hypothesis

We theorize that HA levels may be one of the earliest indicators of Hemangiosarcoma as the function of HA clearance is lost early in the disease process.
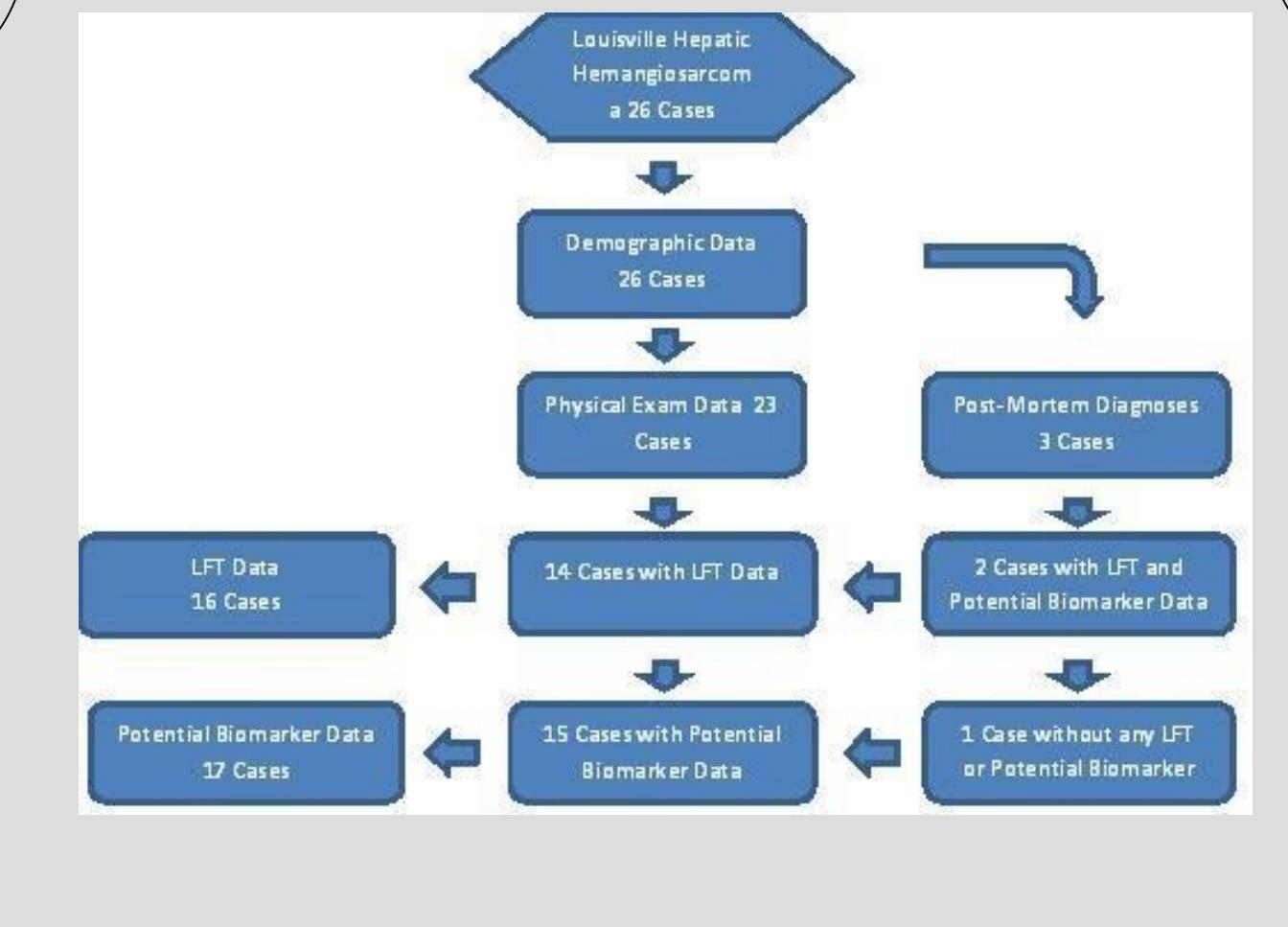
Methods

Samples were obtained from the Hepatobiology COBRE Core Repository. Serum samples were tested for hyaluronic acid levels using a Corgenix ELISA kit (Corgenix, Broomfield, CO) and CK-18 fragment levels determined using Peviva ELISA kits, M65 and M30-Apoptosense (Diapharma, West Chester, OH). Serum cytokines and adipokines were measured using either Milliplex Human Serum Adipokine Panel A and B immunoassay kits (Millipore Corp, Billirica, MA) or a BIO-RAD angiogenesis kit and measured using a Luminex IS 100 system (Luminex Corp, Austin, TX).
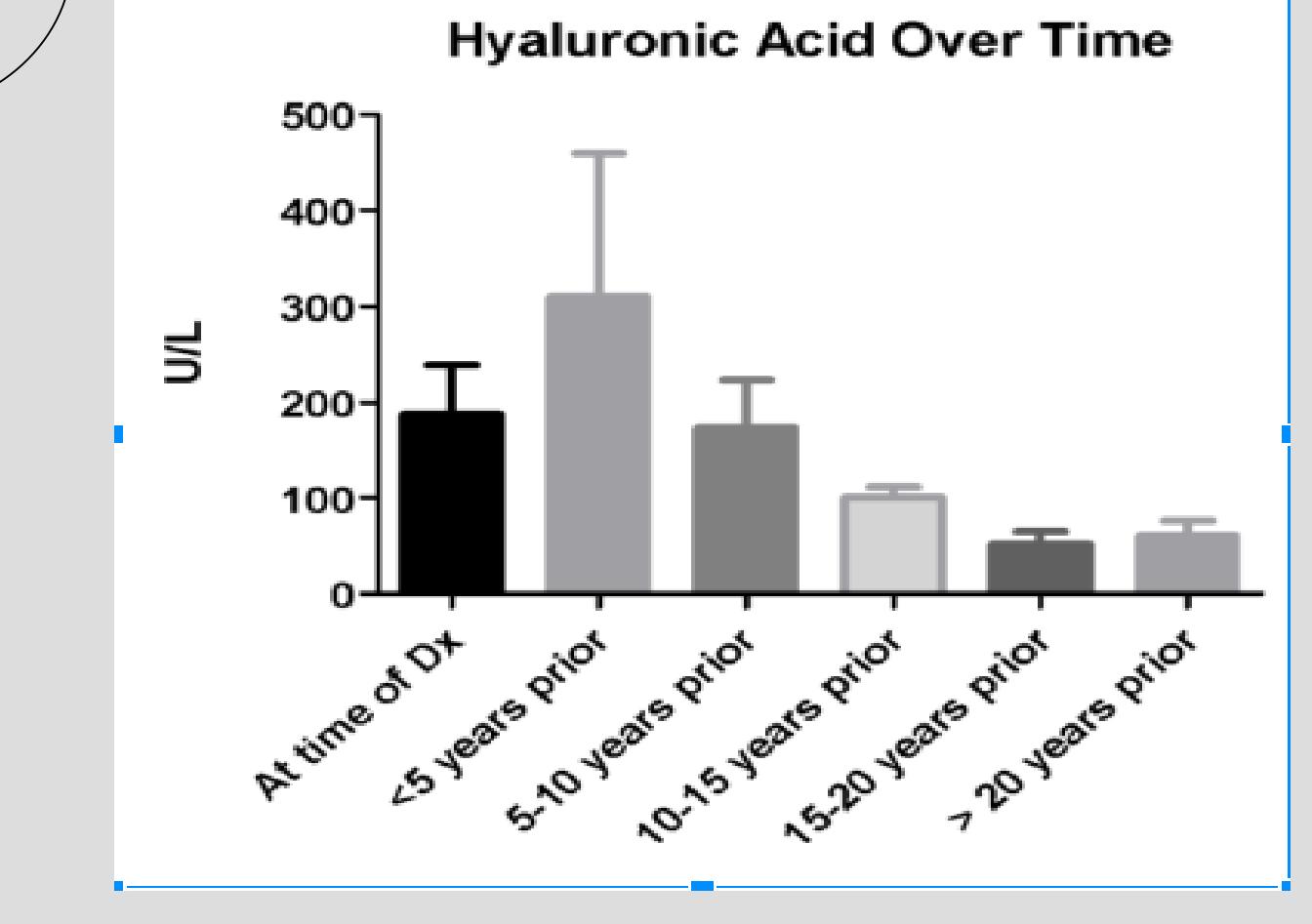
Results

Figure one displays a representative image of a tumor presented in a VC worker that developed Hemangiosarcoma. Figure 2 displays a flowchart of the specimen classification and tests performed. Figure 3 displays the demographic information of the Hepatic Hemangiosarcoma workers and the chemical workers control group.
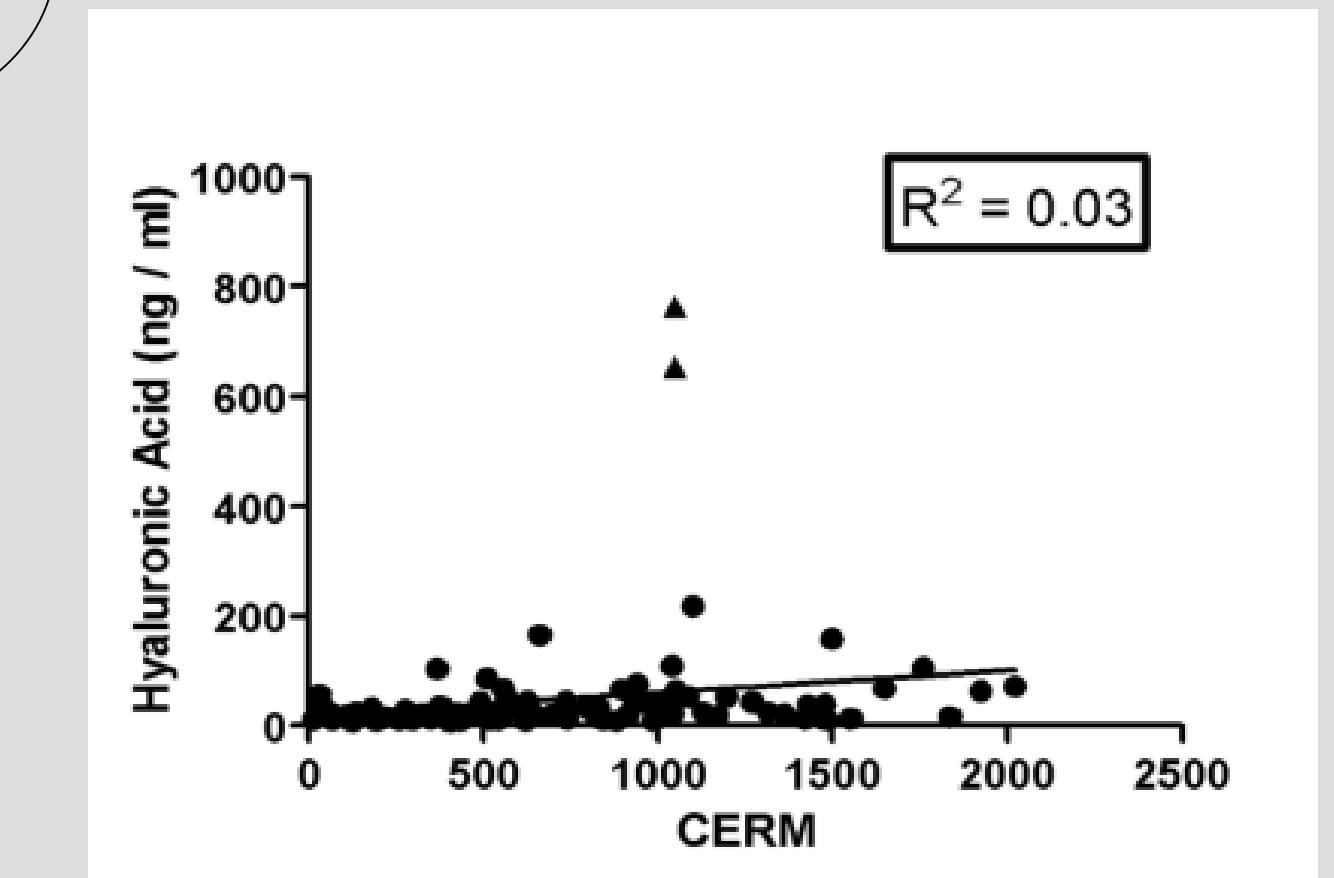

Figure 4 displays lab data for 16 cases (refer to to figure 2). Liver tests were largely normal at time of presentation. Figure 5 displays the mean serum levels of HA that were measured in each HH subject overtime. Figure 6 shows that there was no correlation between cumulative exposure and HA in vinyl chloride workers.

Conclusions

These results demonstrate that HA is a potential biomarker for early detection of HH in workers with industry-related chemical exposure. Elevated levels of HA above the reference range were expressed up to 20 years prior to diagnosis in the workers who later went on to develop HH. Notably, VEG-F levels were lower in HH workers than in their control counterparts. Though cytokines and inflammatory markers may be elevated, such as IL-6 and IL-8, these are non-specific.

Significance

In this study, Hemangiosarcoma workers were generally lean at the time of diagnosis. However, studies have shown that individuals on a high-fat diet with low-exposure may have a significant risk of developing liver disease. Additionally, individuals in developing countries with fewer chemical regulations are at risk of developing HH due to higher rates of exposure to several chemical toxicants.

As lab tests present normal for workers in chemical and plastics plants, routine assessments of HA levels and imaging should be incorporated to decrease mortality rates.

References

1. Cave, M., K. C. Falkner, et al. (2010). "Toxicant-associated steatohepatitis in vinyl chloride workers." Hepatology 51(2): 474-81
2. Creech, J. L., Jr. and M. N. Johnson (1974). "Angiosarcoma of liver in the manufacture of polyvinyl chloride." J Occup Med 16(3): 150-1.
3. Mundt KA, Dell LD, Crawford L, et al. (2017). "Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013." Occup Environ Med 74: 709-716.

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