Cancer Associated Macrophage-Like Cells act as a blood based biomarker for the Early detection of numerous solid tumor types

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ABSTRACT

Filtration of peripheral blood using precision microfilters can act as a “liquid biopsy” to enable the recovery of various cancer associated circulating cells, including a type of circulating stomal cell identified as Cancer Associated Macrophage-Like cell (CAML). CAMLs are phagocytic myeloid cells derived from an immunological response to tumor presence in primary cancer masses. Using a filtration platform, we analyzed the peripheral blood of untreated newly diagnosed cancer patients to ascertain the prevalence of CAMLs. We then screened patients without malignant disease - but positive for a confirmed benign condition, as well as a number of healthy control samples. Our data suggest that CAMLs are highly prevalent in the circulation of newly diagnosed cancer patients, but rare in non-malignant conditions, and absent in healthy individuals.

Figure 1. Isolation and identification of CAMLs by size and nuclear ploidy
(a) CAMLs are easily identified under 10X magnification from a prostate patient
(b) Under 40X magnification the large polyloid nuclear structure can be seen (DAPI). These cells are positive for CD45 and weakly positive for cytokeratin.

INTRODUCTION

CAMLs are specialized myeloid polyloid cells transiting the circulation of patients with various types of solid malignancies and appearing in all stages of cancer1-2. However, while CAMLs are easy to identify by their large size and polyplid nucleus (Fig. 1), their expression of multiple heterogeneous markers has defied conventional characterization and made study difficult using most isolation techniques.

Size exclusion is a technique for isolating large cells from peripheral patient blood irrespective of their surface marker expression. CellSieve™ microfilters efficiently isolate CAMLs and circulating tumor cells (CTCs) from whole blood, making it possible to study both cell types in conjunction with and in relation to malignant disease1-4. CAMLs are especially applicable for early detection of cancer, as demonstrated by a double blind study of breast cancer5.

REFERENCES


RESULTS

CAMLs were found in 85% of cancer patients (n=112/132), in none of the healthy control samples (n=0/51) and in 21% (n=7/33) of patients with benign conditions.

- CAMLs averaged 4 CAMLs per 7.5mL blood samples
- CAMLs were commonly found in stage 1 (81%), stage 2 (88%), and stage 3 (89%) cancers (Fig. 2).
- CAMLs were found in 26% of benign breast masses and in 18% of lupus patients, but in none of the benign breast masses and in 18% of lupus patients.

Figure 2. Percentages of patients positive for CAMLs by stage with CAML sensitivity and specificity

Carcinoma vs Healthy Controls
Sensitivity: 85% (CI95% 78-91%)
Specificity: 100% (CI95% 93-100%)
PPV: 100% (CI95% 100%)
NPV: 72% (CI95% 63-79%)

Carcinoma vs Benign
Sensitivity: 85% (CI95% 78-91%)
Specificity: 79% (CI95% 61-91%)
PPV: 94% (CI95% 89-97%)
NPV: 57% (CI95% 46-67%)

MATERIALS & METHODS

Anonymous peripheral blood was taken from 132 cancer patients [stage I (n=48), stage II (n=51), stage III (n=27), and unknown (n=6)] and from patients with non-metastatic pathologically confirmed breast (n=17), esophageal (n=24), lung (n=30), prostate (n=37), and pancreas cancers (n=24). Further, anonymous blood was taken from patients with confirmed non-malignant conditions including benign breast masses (n=19), lupus (n=11), and benign prostatic hyperplasia (n=3), and from healthy control volunteers (n=51). CAMLs were isolated from whole peripheral blood by the CellSieve™ microfiltration technique at 3 institutions and stained for cytokeratin 8, 18, & 19, CD14 and CD45. CAMLs were defined as enlarged, multinuclear cells with diffuse cytoplasmic cytokeratin and/or CD45/CD14 positive.

CONCLUSIONS

- CAMLs are a sensitive and specific blood based biomarker for the early detection of multiple solid tumors.
- CAMLs were not found in healthy individuals and were uncommon in people with benign conditions.
- Additional large scale studies should be undertaken to validate these preliminary results and determine use in other malignant diseases.

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