To the editor:

**MGUS prevalence in an ethnically Chinese population in Hong Kong**

Recent data suggest that the incidence of multiple myeloma may be increasing in Taiwan over the past 25 years, which elevates concern that myeloma incidence may be increasing in Asia. If true, this may reflect changes in lifestyle, occupational and environmental exposures, and food intake among other factors, between the younger and older birth cohorts. However, this observation could also be indicative of differences in access to health care, improvement in diagnostic techniques, data collection method, and other influences unrelated to biology.

Based on a large prospective cancer-screening trial (N = 77,469), we have shown that multiple myeloma is consistently preceded by a precursor state: monoclonal gammopathy of undetermined significance (MGUS). To address the question of whether multiple myeloma is becoming increasingly more common in Asia, and to overcome the above-mentioned potential bias due to factors unrelated to biology, we conducted a population-screening study to determine the prevalence of MGUS in an ethnically Chinese population.

Plasma from 500 male and 500 female volunteer donors 50 years of age or older (median, 57 years; range, 50-65 years) was collected following a uniform protocol at the Hong Kong Red Cross Blood Transfusion Service from December 2008 to January 2009. Using serum protein electrophoresis (SPEP) (Helena SPIFE 3000; Helena Laboratories, Beaumont, TX) and κ and λ free light chain (FLC) assays (SPA-Plus; The Binding Site, Birmingham, United Kingdom), we assessed for evidence of monoclonal (M) proteins and abnormal FLC ratios (normal reference, 0.26-1.65) for all patients. Patients with an abnormal FLC ratio and/or suspicious SPEP (28 male, 10 female) were subjected to immunofixation electrophoresis.

Among screened subjects we found that 6 of 500 men (1.2%) and 2 of 500 women (0.4%) had MGUS; overall, this represents a prevalence of 0.8% (95% confidence interval [CI]: 0.3%-1.4%). All study subjects had an immunoglobulin G (IgG) isotype monoclonal band except for 2 individuals: 1 with IgA and another with bicalonal IgG (Table 1).

To our knowledge, our study represents the first larger, prospective population-screening study of MGUS in ethnically Chinese persons. Our findings are consistent with older studies showing that Asians have a fivefold lower incidence of multiple myeloma compared with whites, and are consistent with prior MGUS prevalence studies in Thailand (2.3%; 95% CI, 1.1%-4.6%), Korea (3.3%; 95% CI, 1.0%-4.2%), and Japan (2.1%; 95% CI, 1.9%-2.2%). In the Olmsted County study conducted by the Mayo Clinic, the prevalence of MGUS among 50- to 59-year-old and 60- to 69-year-old whites was 1.6% and 3.0%, respectively. Although the number of index cases in our study is low, the gender ratio is also well maintained. We speculate that underlying mechanisms accounting for the variance in prevalence of MGUS and multiple myeloma among different ethnic groups is most likely due to differences in germline genes, environmental exposures, and lifestyle.

The large, aging population of China urgently needs data on the possible future incidence of multiple myeloma. Our results support the hypothesis that a lower incidence of multiple myeloma in ethnic Chinese people is maintained at early disease initiation and not due to different rates of disease progression. The lifestyle and economic status of various screened Asian populations are not uniform and such observation comes from a highly Westernized and developed population of ethnic Chinese individuals.

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**Table 1. Study subjects with evidence of an M protein**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>M-protein isotype</th>
<th>M-protein concentration, g/dL</th>
<th>Free κ, mg/dL</th>
<th>Free λ, mg/dL</th>
<th>FLC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>59</td>
<td>IgG κ</td>
<td>0.22</td>
<td>6.76</td>
<td>11.05</td>
<td>0.61</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>53</td>
<td>IgG λ</td>
<td>0.60</td>
<td>8.65</td>
<td>12.24</td>
<td>0.71</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>50</td>
<td>IgG κ</td>
<td>0.54</td>
<td>15.09</td>
<td>11.46</td>
<td>1.32</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>54</td>
<td>IgG κ</td>
<td>0.39</td>
<td>21.76</td>
<td>14.91</td>
<td>1.46</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>Bicalonal (IgG κ and IgG λ)</td>
<td>0.57, 0.62</td>
<td>14.09</td>
<td>11.59</td>
<td>1.22</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>IgG λ</td>
<td>1.45</td>
<td>6.28</td>
<td>285.64</td>
<td>0.02</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>IgG κ</td>
<td>1.89</td>
<td>18.64</td>
<td>11.26</td>
<td>1.66</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>56</td>
<td>IgG λ</td>
<td>0.47</td>
<td>6.14</td>
<td>11.63</td>
<td>0.53</td>
</tr>
</tbody>
</table>

These results are based on screening of 500 men and 500 women (50 years of age or older) in an ethnically Chinese population in Hong Kong, and support the fact that Chinese individuals in Hong Kong have lower incidence of MGUS than whites. The minimal number of samples required to distinguish 0.8% (our study proportion) from 3% (lower bound of reported prevalence of MGUS in whites) is 448 (power [β] = 90%; specificity [α] = 95% 2-tailed; test: 1-sample χ²).
Lymphocytic variant hypereosinophilic syndrome (LHES) is a rare disease in which cytokine production by T cells drives blood and tissue eosinophilia.1,2 We report a case of LHES in a patient with chronic active Epstein-Barr virus (CAEBV) infection and an EBV-infected T-cell clone producing eosinophilopoietic cytokines. All methods can be found in supplemental Methods (available on the Blood Web site; see the Supplemental Materials link at the top of the online article).

A 64-year-old man presented with a 2-year history of pruritic plaques on the extremities, trunk, and face, and that ulcerated and formed eschars with residual scarring (Figure 1A left and center panels). Laboratory testing revealed eosinophilia (51,111/mm3), elevated serum immunoglobulin E (IgE) (13,995 ng/mL), and a slightly elevated serum immunoglobulin G (IgG) (12,140 mg/dL). Cytogenetic studies and testing for cytokines (interleukin-4 [IL-4], IL-5, IL-13) (Figure 1B) revealed no abnormalities. Bone marrow biopsy (Figure 2) showed increased percentage of V5.1-positive T cells producing Th2 cytokines (interleukin-4 [IL-4], IL-5, IL-13) (Figure 1B). Bone marrow biopsy was normocellular with eosinophilia and no lymphocytosis. Cyto genetic studies and testing for FIP1L1/PDGFRα were negative.

Quantitative EBV DNA polymerase chain reaction (PCR) showed 147,000 copies per mL of blood (normal <200) with the highest levels in T cells (79,891 copies per million T cells, 15,675 copies per million B cells, and 38,376 copies per million non-T, non-B cells). EBV DNA was localized in 70% of V5.1-positive T cells at 8 to 25 copies per cell (Figure 1E), and DNA from sorted V5.1-positive T cells showed a single band on Southern blot using a probe to the EBV terminal repeats, indicating that the virus infecting the V5.1-positive T cells was clonal (supplemental Figure 3). Skin biopsy prior to therapy showed eosinophilic infiltration and EBV-encoded RNA (EBER) staining consistent with EBV RNA in T cells (Figure 1D).

To the editor:

Chronic active Epstein-Barr virus infection: a novel cause of lymphocytic variant hypereosinophilic syndrome

S.P.W. and A.M. contributed equally to the work.

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The study was approved by institutional review boards at Queen Mary Hospital. This study was exempt from institutional review, board review, and informed consent as per the National Institutes of Health Office of Human Subjects Research because it analyzed existing samples and data stripped of personal identifiers and there was no patient contact.

Contribution: S.P.W. analyzed data and drafted the report; A.M., R.C., and A.Z. designed research, processed samples, and ran arrays; C.-K.L. and W.-Y.A. enrolled patients and designed research; O.L. designed the research, analyzed data, and drafted the report; and all authors reviewed the manuscript, gave input, and approved the final version.

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References


Scattered EBV-positive cells were also noted in the bone marrow biopsy (supplemental Figure 4).

Prednisone resulted in improvement in skin lesions (Figure 1A right panel) and eosinophilia, but had no effect on EBV DNA levels (Figure 1C). Biopsy of a papular lesion showed a clonal EBV-positive T-cell infiltrate consistent with hydroa vacciniforme. Interferon-α (IFN-α), lenalidomide, and vorinostat and valganciclovir were ineffective in reducing the EBV viral load, and the patient continues on prednisone 10 mg daily.

EBV DNA PCR was performed using peripheral blood from 15 subjects with LHES and 31 normal volunteers (Figure 1F). Slightly elevated EBV DNA levels (3100, 1650, and 5800 copies per mL) were detected in 1 normal subject and 2 patients with LHES, 1 of whom had pruritic skin lesions. Retesting of blood from this patient was again positive at 11,800 copies per mL, but EBER staining of skin and bone marrow biopsies was negative.

Although our patient meets criteria for CAEBV disease based on the chronic presence of high levels of EBV in the blood, skin, and bone marrow,3,4 his clinical presentation was atypical and more consistent with LHES with peripheral and tissue eosinophilia caused by an EBV-infected V5.1 T-cell clone producing Th2 cytokines. Although EBV is not a common cause of LHES, screening for EBV infection should be considered in patients presenting with eosinophilia and a T-cell clone.

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MGUS prevalence in an ethnically Chinese population in Hong Kong

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