Correspondence

To the editor:

T-cell clonality of undetermined significance

We read with great interest the report of Delfau-Larue et al1 on the ongoing discussion about the significance of dominant T-cell clones as a hallmark of T-cell malignancy. The authors showed the occurrence of dominant T-cell clones in the peripheral blood of patients with cutaneous T-cell lymphoma (CTCL) (30%), non-CTCL-related skin diseases (41%), and other benign infiltrates (34%). From these findings, they conclude that demonstration of T-cell clonality in the peripheral blood is not of undetermined significance, but of no significance at all. Based on our own results, we wish to point out the view shared by many investigators using polymerase chain reaction (PCR) for clonality studies: that, with some technical precautions taken, T-cell receptor gene rearrangement analysis is reliable and specific and may considerably add to the diagnosis of malignant lymphoproliferative disorders, even in peripheral blood.

We are well aware that expansion of T-cell clones is a prerequisite for antigen-specific T-cell responses and that T-cell clones may be present under many reactive conditions. Therefore, it is not surprising that different PCR-based methods are able to amplify dominant T-cell clones with varying frequency depending on their sensitivity. We have shown that overinterpretation of these dominant PCR products with respect to the diagnosis of malignancy can be avoided by repeated independent PCR determinations of the same samples and application of high resolution separation techniques such as GeneScan analysis and/or sequencing.2 Under reactive conditions dominant PCR products vary, whereas under malignant conditions dominant PCR products are exactly reproducible. Our investigation of 21 clear-cut benign skin infiltrates (psoriasis and contact dermatitis) revealed dominant T-cell clones in only 3 cases. Repeated PCR and GeneScan analyses of these 3 samples demonstrated that the dominant amplificates were of different size, indicating the presence of several different predominant T-cell clones in these lesions. Therefore, we decided to consider cases that do not show identical dominant PCR products in repeated PCR analyses of the same sample as pseudo monoclonal.

Here, we show that this holds also true for peripheral blood samples of patients with cutaneous T-cell lymphoma (CTCL), parapsoriasis, and pseudo T-cell lymphoma (Table 1). Similar to the results of Delfau-Larue et al, 19 of 30 cases (63%) of parapsoriasis and pseudo T-cell lymphoma showed a dominant T-cell clone in the peripheral blood at prima vista analysis. But repeated analysis of these samples revealed PCR products of different size, that is, pseudo monoclonality, in all but 1 of the samples, so that the truly monoclonal cases in these nonmalignant conditions amounted to just 3.3%. In stage IV CTCL patients, the opposite picture appeared: the prima vista dominant PCR products seen in 9 of 11 patients (81.8%) were confirmed by repeated analysis of the same sample. In addition, identical amplificates were generated from lesional skin and peripheral blood samples in these 9 patients, further confirming T-cell clonality in different lymphocyte recirculation compartments as expected from T-cell malignancies. In contrast, true T-cell clonality is a very rare finding under nonmalignant conditions; in such cases, the term “T-cell clonality of undetermined significance” should be reserved, in analogy to the term “monoclonal gammopathy of undetermined significance.” In the study by Delfau-Larue et al, only 6% of 211 patients with non-CTCL lesions showed the same clonal T-cell population (of undetermined significance) after denaturing gradient gel electrophoresis (DGGE) analysis in skin and peripheral blood; the identity of the comigrating bands, however, should be confirmed by an independent assay with higher resolution such as GeneScan analysis or sequencing.3 Patients with clinically clear-cut nonmalignant conditions and confirmed T-cell clonality should be carefully documented and followed to further determine the natural course of T-cell clonality of undetermined significance.

In summary, we wish to suggest that “dominant T-cell clone”1 is a rather technical term of still unknown clinical relevance which should be interpreted carefully. The term “clonality”1 should only be used when pseudo monoclonality has been excluded by repeated independent PCR determinations. Under these considerations, the analysis of peripheral blood samples of patients suffering from cutaneous T-cell lymphoproliferative diseases is of high diagnostic value.

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Table 1. T-cell clonality in the peripheral blood of 49 patients with cutaneous T-cell lymphoma, parapsoriasis, and pseudo T-cell lymphoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Dominant clone</th>
<th>Oligo/polyclonality</th>
<th>Pseudo monoclonality</th>
<th>Monoclonality</th>
<th>Identical clone in skin and PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages Ia-III†</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage IV†</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Parapsoriasis‡</td>
<td>15</td>
<td>11</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Pseudo T-cell lymphoma§</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Analysis is TCR-PCR and GeneScan analysis. ND, not determined.
†CTCL confined to the skin.
‡CTCL with lymph node involvement.
§Small plaque parapsoriasis, n = 5; large plaque parapsoriasis, n = 7; lichenoid parapsoriasis, n = 3.
§Lymphocytic infiltration of the skin.
Response:

Peripheral blood T-cell clonality of no cutaneous T-cell lymphoma diagnostic value

I thank Dr Dippel and his colleagues for their comments on our report concerning the diagnostic value of peripheral blood (PB) T-cell clonality in clinical suspicion of CTCL. We have argued that demonstration of T-cell clonality in PB is of unknown significance (not "of no significance") and, more precisely, that it has no CTCL diagnostic value as long as the same clone has not been identified in the skin (in contrast to Gene Scan analysis, DGGE migration of PCR products depends on CDR3 sequences and not only on CDR3 size). By contrast, identification of the same clone in skin and blood is of high diagnostic value.

As Dippel et al remind us, PB T-cell clonal expansions occur in multiple clinical settings. For example, peripheral blood expansion of CD8+ clones have been described in healthy individuals, as well as in patients with rheumatoid arthritis, and have been shown to be remarkably stable over time (up to 4 years). They increased with age in both the CD45RA+ (naive or long-life memory cells) and CD45RO+ (memory) compartments. Accordingly, it has been our experience that, using PCR-DGGE, we detect a T-cell clone, dominant over polyclonal background, in the blood of 30% to 40% of studied patients, whether with cutaneous malignancy or benign disease. Moreover, dominant T-cell clones are increasingly detected with age, and once detected in a given patient, the T-cell clone remained detectable on all 2001 serial samples with a follow-up as long as 6 years (unpublished data, 2001).

Finally, although Dippel et al’s concept of "pseudoclonality" seems to us of no physiologic relevance, we agree with them that the study of peripheral blood samples in patients with a suspicion of CTCL is helpful for the diagnosis as long as the same T-cell clone is detectable in both skin and blood samples.

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References


To the editor:

Homzygous gene conversion in von Willebrand factor gene as a cause of type 3 von Willebrand disease and predisposition to inhibitor development

Von Willebrand disease (VWD) is the commonest congenital bleeding disorder, with a prevalence, estimated from population studies, of about 1%, although the prevalence of patients requiring treatment is much lower. This autosomal inherited disorder is caused by either qualitative (type 2) or quantitative (type 1 and 3) deficiency of von Willebrand factor (VWF). The human VWF gene is located on chromosome 12 and consists of 52 exons. A pseudogene on chromosome 22 has also been identified, which is 21-29 kb in length and corresponds to exons 23-34 of the VWF gene. It has 97% homology to the authentic VWF gene, but the presence of multiple stop codons on the pseudogene indicates that this is not a functional gene in humans.

In recent years, many molecular defects of the VWF gene have been identified in patients with VWD. Molecular defects in types 1 and 3 VWD are not confined to specific regions of the gene, as in type 2 VWD. The reported molecular defects that have caused autosomal recessive severe type 3 VWD are large gene deletions, frameshift mutations, nonsense mutations, splice-site mutations, defects at the level of mRNA expression, and some candidate rearrangement by PCR-based GeneScan analysis in advanced cutaneous T-cell lymphoma: a critical evaluation. J Pathol. 1999;188:146-154.

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plasma VWF:Ag multimers. DNA and RNA were extracted from the propositus and parents to carry out genotypic studies. Haplotypes of parents and propositus were determined by analysis of 2 polymorphic regions of the tetranucleotide (ATCT) simple repeat in intron 20 (VNTR I and II) of the VWF gene, along with 2 restriction fragment length polymorphisms (RFLP) of the VWF gene. These gene-tracking studies showed that the boy had inherited the same affected allele from each parent. The whole VWF gene was screened for mutations using chemical cleavage mismatch detection (CCMD) analysis. Any indication of sequence changes was investigated by sequencing.

CCMD of exon 28 revealed multiple mismatched bands. The sequencing of this exon revealed a gene conversion to have taken place, for which the boy is homozygous and the parents are heterozygous (see Figure 1). Five base changes corresponding to the pseudogene sequence were identified: 4181C>T, 4201C>T, 4277A>G, 4329T>C, and 4355T>A. The maximal length of the conversion is approximately 299 bp, and the minimal length is 173 bp. The first base change (4181C>T) results in a stop codon, which would result in premature termination of the protein. The nucleotides are numbered from the major transcription cap site (+1), which is located 250 nucleotides upstream of the first nucleotide in the ATG initiation codon. Amino acid residues are numbered from the ATG initiation codon (residue 1) to the carboxy-terminal lysine (residue 2813) of pre-pro-VWF. All changes identified in the VWF gene of the parents and the propositus were confirmed by DNA sequencing and then by restriction enzyme analysis. Two possible factors may contribute to the occurrence of a gene conversion. First, the divergence between the pseudogene and the VWF gene is 3.14%, and the divergence between them for sequences corresponding to exons 23-34 is 2.47%. Homology between the 2 genes is greatest in these exonic regions and may contribute to recombinations. Second, it is hypothesized that a chi sequence or sequence similar to a chi sequence can regulate homologous recombinations. There are 2 consensus chi sequences (5'-GCTGGTTGG-3') around the region of this gene conversion (one in exon 28 and the other in intron 27), which may be responsible for the relatively frequent gene conversion events in exon 28. Six other cases of homologous gene conversion have been reported previously to be the cause of VWD type 1 or type 2B in 5 unrelated families. A Q1311 mutation has also recently been detected in the homozygous state in 4 Spanish patients from 2 apparently unrelated families of gypsy origin.

The rest of the VWF gene was screened by investigating six overlapping mRNA segments. Another point mutation was found in exon 49, a 8363G>A substitution, which would predict G2705R. This was confirmed in the DNA to be homozygous in the propositus and heterozygous in the parents, suggesting that it be on the same allele as the gene conversion. As the gene conversion is upstream of this mutation and generates a stop codon, this point mutation would not be translated.

In conclusion, we have investigated a boy with severe type 3 VWD who is homozygous for a gene conversion in exon 28 that results in premature termination of the protein. The asymptomatic parents, who are first cousins, are heterozygous for the same mutation. It can be speculated that this mutation produces a truncated dysfunctional protein lacking many of the essential functional sites of VWF. In a patient homozygous for this mutation, the protein cannot be assembled and, therefore, will not be secreted and will be absent from the patient’s plasma.

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13. Jenkins PV. Screening for candidate mutations causing von Willebrand’s disease (vWD). In: DJ Perry, JK Psaila, eds. Methods of Molecular Medicine: Hemo-
To the editor:

A rapid and reliable 7-deletion multiplex polymerase chain reaction assay for α-thalassemia

The molecular genetics of the α-thalassemias has been comprehensively reviewed.1 Of the numerous mutations that have been described, deletions at the α-globin gene locus account for the vast majority of α-thalassemia alleles.2 The most widely occurring of these are the -α3.7 and -α4.2 single α-globin gene deletions, while double α-globin gene deletions in cis, such as the -SEα, -FL and -THα alleles are very common within Southeast Asia, and the -MED and -α20.5 double-gene deletions occur more frequently in the Mediterranean area.

Since the publication of the entire sequence of the human α-globin gene cluster,3 we and others have developed multiplex polymerase chain reaction (PCR) methods to diagnose different subsets of α-thalassemia deleterional determinants.4,5 Generally, however, the high G+C nucleotide content and high degree of homology between the genes and pseudogenes at this locus have made it technically challenging to develop a multiplex PCR assay capable of detecting all 7 of the above mutations [-α3.7, -α4.2, -SEα, -FL, -MED, -(α)20.5, and -THα] in a single reaction. We have now successfully developed an improved single-tube multiplex PCR assay that can detect heterozygosity, homozygosity, and compound heterozygosity of these 7 α-globin gene deletions.

To achieve this, several aspects of our original multiplex PCR assay were modified. These included the redesign of several primers, inclusion of additional new primers, reoptimization of primer concentrations, and use of a different, chemically modified automatic hot-start DNA polymerase. Each 50-μL reaction contained 200 μM of each dNTP, 1.5 mM MgCl2, 1 × Q-solution (Qiagen, Hilden, Germany), 2.5 U HotStarTaq DNA polymerase in supplied reaction buffer (Qiagen), 100-200 ng of genomic DNA, and 16 different primers at various concentrations (Table 1). Reactions were conducted in a T3 thermal cycler (Biometra, Göttingen, Germany), with an initial 15-minute denaturation at 96°C, followed by 30 cycles of 98°C denaturation for 45 seconds, 60°C annealing for 90 seconds, and 72°C extension for 135 seconds. A final 5-minute extension at 72°C completed the reaction. Ten microliters of each amplified product was analyzed by electrophoresis through a 1% agarose gel in 1× Tris-Borate-EDTA buffer at 10 volts/cm for an hour. The expected amplicon sizes for each of the deletion junction fragments and the control α2 globin gene and LIS1 gene 3′ untranslated region (UTR) fragments are listed in Table 1. Because any of the 7 deletions either partially or completely removes the α2 globin gene, its positive amplification serves to indicate heterozygosity when a deletion allele is also present. The LIS1 gene 3′ UTR fragment serves as a separate control for general amplification success. Multiplex PCR results from representative DNA samples with various α-thalassemia genotypes are shown in Figure 1.

This simple assay has been validated on over two hundred DNA samples from α-thalassemia-1 and HbH disease individuals, and represents a rapid and reliable method for detecting 7 of the most common mutations of α-thalassemia.

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Supported by Singapore grant NMPR/0365/1999 to S.S.C.

Table 1. Primer sequences for α-thalassemia multiplex PCR and expected amplicon sizes

<table>
<thead>
<tr>
<th>Name</th>
<th>5′ → 3′ sequence</th>
<th>GenBank ID: nucleotides</th>
<th>Concentration</th>
<th>Amplicon (size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIS1-F</td>
<td>ATACCATGTTACCCCATCAGG</td>
<td>HSLS10:510→532</td>
<td>0.5 μM</td>
<td>LIS1 3′ UTR fragment (2350 bp)</td>
</tr>
<tr>
<td>LIS1-R</td>
<td>AGGCTTTCATCAATGTCAGCC</td>
<td>HSLS10:2869→2838</td>
<td>0.5 μM</td>
<td>-α2 globin fragment (2022/2029 bp)</td>
</tr>
<tr>
<td>α2.3.7-F</td>
<td>CCCCCGCCAGAACGTCACCC</td>
<td>HUMHBA4:5676→5694</td>
<td>0.2 μM</td>
<td>-α3.7 junction fragment (1967 bp)</td>
</tr>
<tr>
<td>3.7/20.5-R</td>
<td>AAGCGACTTCTAGGTACCACG</td>
<td>HUMHBA4:11514→11494</td>
<td>0.2 μM</td>
<td>-α2 globin gene (1800 bp)</td>
</tr>
<tr>
<td>α2.3.7-F</td>
<td>As above</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>α2-R</td>
<td>AGAACAGGAGAAGCGGCGGTG</td>
<td>HUMHBA4:7474→7475</td>
<td>0.2 μM</td>
<td>-α2 globin gene (1800 bp)</td>
</tr>
<tr>
<td>4.2-F</td>
<td>GTTTTACCCCATGTTGCTC</td>
<td>HUMHBA4:3086→3084</td>
<td>0.5 μM</td>
<td>-α4.2 junction fragment (1628 bp)</td>
</tr>
<tr>
<td>4.2-R</td>
<td>CCGCTTGATCTTTGACTTCCC</td>
<td>HUMHBA4:8942→8920</td>
<td>0.5 μM</td>
<td>-α20.5 junction fragment (1349 bp)</td>
</tr>
<tr>
<td>SEA-F</td>
<td>GAGATGCGATGCGATGCCG</td>
<td>HSGG1:26120→26140</td>
<td>0.2 μM</td>
<td>-SEA junction fragment (1153 bp)</td>
</tr>
<tr>
<td>SEA-R</td>
<td>AGCAGGATGCGATGCGATGCCG</td>
<td>HSCOS12:1241→1221</td>
<td>0.2 μM</td>
<td>-SEA junction fragment (1153 bp)</td>
</tr>
<tr>
<td>THAI-F</td>
<td>GACCTTTCTCAGGCGCTG</td>
<td>HSGG1:9952→9612</td>
<td>0.3 μM</td>
<td>—</td>
</tr>
<tr>
<td>THAI-R</td>
<td>CAAATGCGGACTGACGACGACTG</td>
<td>HSCOS12:3817→3797</td>
<td>0.2 μM</td>
<td>—</td>
</tr>
<tr>
<td>20.5-F</td>
<td>GCCCAATACGGAGAGATAGCTG</td>
<td>HSGG1:17904→17924</td>
<td>0.2 μM</td>
<td>-α20.5 junction fragment (1007 bp)</td>
</tr>
<tr>
<td>20.5-R</td>
<td>As above</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MED-F</td>
<td>TACCTTTGAGAACACAGATC</td>
<td>HSGG1:23123→23144</td>
<td>0.2 μM</td>
<td>-MED junction fragment (807 bp)</td>
</tr>
<tr>
<td>MED-R</td>
<td>TACATGCTGACAGCCTGAC</td>
<td>HSGG1:41183</td>
<td>0.2 μM</td>
<td>—</td>
</tr>
<tr>
<td>FIL-F</td>
<td>TTTAAATGCGAAACAGGGCAG</td>
<td>HSGG1:12320→12327</td>
<td>1.0 μM</td>
<td>-FL junction fragment (546 bp)</td>
</tr>
<tr>
<td>FIL-R</td>
<td>ATAACCTTATCAGGACCTATGACG</td>
<td>HSCOS12:570→546</td>
<td>1.0 μM</td>
<td>—</td>
</tr>
</tbody>
</table>

jxn, junction.
Figure 1. Strategy and results of α-thalassemia multiplex polymerase chain reaction analysis. (A) Schematic representation of the α-globin gene cluster, indicating extents of the 7 deletions and relative positions of the primers (except for the control LIS1-F and LIS1-R primers, which are located on a different chromosome). Locations of X, Y, and Z sequence homology boxes and hypervariable regions (HVRs) are also shown. (B) Multiplex PCR results from genomic DNA samples with various α-globin genotypes. M indicates Generuler 1kb DNA ladder (Fermentas, St Leon-Rot, Germany).

References

To the editor:

Improve or abandon the standardized response criteria for myelodysplastic syndromes recommended by the International Working Group

Standardizing any aspect of a disease as clinically and biologically heterogeneous as the myelodysplastic syndromes (MDSs), whose natural history is not infrequently confounded by wide fluctuations in the peripheral blood (PB) indexes and where therapeutic options range from a simple watch-and-wait policy to stem cell transplantation, is a formidable task. Previous attempts of international experts to define some aspects of this cryptic disease include the French-American-British classification (FAB), the World Health Organization classification (WHO), and the International Prognostic Scoring System (IPSS). The latest in this series is a publication from the International Working Group (IWG) detailing standardized criteria to be used for response evaluation in MDS. First of all, the attempt must be lauded. It is a welcome and timely step, especially for those of us whose papers reporting the results of clinical trials have been returned over and over because the reviewer’s idea of a response did not match the investigator’s. Unfortunately, in keeping with many previous exercises to harness the complexity of MDS, the IWG’s current proposal is also deficient despite attempts to appear comprehensive by including the more subtle issues such as emotional, social, and/or spiritual improvements in quality of life. Below are some of the most immediate practical problems encountered in applying these recommendations to a real-life situation.

Nowhere in this detailed document does it specify how to calculate either the baseline or intratherapy values for hemoglobin, absolute neutrophil count (ANC), or platelets. Should a single pretherapy absolute complete blood count (CBC) be used as the gold standard against which to measure response, or should this value be a derivative of many weekly counts? And if the latter, then how many weeks should one consider appropriate as being representative? Similarly, how should one calculate transfusion dependency? I may call a patient transfusion dependent if they received even a single transfusion in the preceding 2 months. Should that make them transfusion independent if they did not receive another for 9 weeks after starting therapy? The confusion is even worse when one tries to handle weekly CBCs during the course of therapy. It is recommended that studies should prospectively assess whether there is a difference in outcome from 0 to 6 months, 6 to 12 months, and longer than 12 months from the diagnosis of MDS. It sounds eminently sensible, except when one tries to actually use these recommendations practically. Should an average value of CBCs obtained over 6-month periods be used for these calculations, or should an absolute value closest to the specified times be the standard? Or perhaps a combination of both may be better? What should these values be compared with? A single pretherapy CBC or an average of many? And what about transfusions?

Recently, the responses of patients treated on one of our protocols were evaluated by ourselves and by 2 independent groups. While all 3 evaluators agreed that a significant proportion of the patients responded to the therapy, the specific percent responders according to the 2 independent groups who used IWG response criteria was different. The major stumbling block was a...
lack of specific criteria for establishing baseline parameter levels and for identifying the intratherapy values that should be used for response assessment.

Another problem is related to the interpretation of subtle differences between the responses of individual patients. Consider for example, the variations between just 2 patients whose responses according to the new criteria might read something like “PR, cytogenetics minor, HI-E major transfusion, HI-E minor Hb, HI-P minor, HI-N major,” versus “PR, cytogenetics minor (by FISH only), HI-E minor transfusion, HI-E major Hb, HI-P major, HI-N minor.” Are these 2 responders really different, and if so, among 20 responders, what is the likelihood of having 20 different types of responses with minor variations? Further, are not these greatly expanded numbers of variables likely to affect \( P \) values and the interpretation of what constitutes significance? How is this supposed to introduce uniformity in the interpretation of results?

I would like to suggest that, before making such detailed recommendations with the serious intent for universal application, the writers of these types of classifications should make an attempt to apply their recommendations to a practical situation, since at least their obvious deficiencies would be immediately apparent. The IWG paper\(^1\) would have been far more significant if the authors had included an analysis of an actual clinical trial to back the significance and universal utility of their recommendations. Failure to do so has resulted in adding to the confusion in an already complex situation. By neglecting to standardize baseline, as well as intratherapy, values of blood counts that must be used for response assessment, the IWG projects an image of a body far removed from patient care and evaluation of clinical trials. Rather, their recommendations appear to be a patchwork representing the unique interests of a few individual IWG participants. This situation is analogous to the ancient parable in the Upanishads where descriptions of an unseen elephant varied widely depending upon which part the narrator felt through a curtain. Perhaps it is time to address the ultimate Schrödinger-type interrogative: what constitutes MDS? I suggest that it is more prudent to consider refractory anemia, refractory anemia with ring sideroblasts, refractory anemia with excess of blasts, and chronic myelomonocytic leukemia as 4 distinct disorders, thereby simplifying interpretation of both biologic and clinical studies.

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Reference

T-cell clonality of undetermined significance

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